

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
21 October 2004 (21.10.2004)

PCT

(10) International Publication Number
WO 2004/089885 A1

(51) International Patent Classification⁷: **C07C 317/22**, 317/28, 59/48, C07D 215/18, 239/24, 213/71, A61K 31/10, 31/192

(21) International Application Number:
PCT/SE2004/000535

(22) International Filing Date: 6 April 2004 (06.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0301010-5 7 April 2003 (07.04.2003) SE

(71) Applicant (for all designated States except US): **ASTRAZENECA AB [SE/SE]**; Södertälje, 151 85 (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BONNERT, Roger** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **BROUGH, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **DAVIES, Andrew** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **LUKER, Timothy** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **MCINALLY, Thomas** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **MILLICHIP, Ian** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **PAIRAUDEAU, Garry** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **PATEL, Anil** [GB/GB];

AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **RASUL, Rukhsana** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **THOM, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S- 151 85 Södertälje (SE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

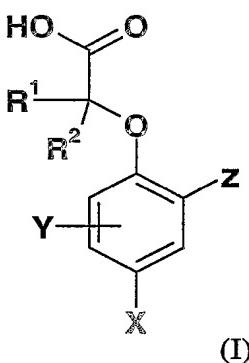
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS



(57) Abstract: The invention relates to substituted phenoxyacetic acids (I) as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

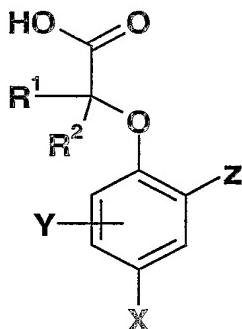
WO 2004/089885 A1

NOVEL COMPOUNDS

The present invention relates to substituted phenoxyacetic acids as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has been found that certain phenoxyacetic acids are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which:

X is halogen, cyano, nitro, $S(O)_nR^6$ or $C_{1-4}alkyl$ which is substituted by one or more halogen atoms;

Y is selected from hydrogen, halogen, CN, nitro, SO_2R^3 , OR^4 , SR^4 , SOR^3 , $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5 , $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3 , C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or $C_{1-6}alkyl$, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7 , $S(O)_nR^6$ where n is 0, 1 or 2;

Z is aryl or a ring A, where A is a six membered heterocyclic aromatic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicyclic containing one or more O, N,

S atoms, the aryl or A rings all being optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, OH, SH, nitro, COR⁹, CO₂R⁶, SO₂R⁹, OR⁹, SR⁹, SOR⁹, SO₂NR¹⁰R¹¹, CONR¹⁰R¹¹, NR¹⁰R¹¹, NHSO₂R⁹, NR⁹SO₂R⁹, NR⁶CO₂R⁶, NHCOR⁹, NR⁹COR⁹, NR⁶CONR⁴R⁵, NR⁶SO₂NR⁴R⁵, aryl, heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl or C₁-alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶, NR⁶R⁷, S(O)_nR⁶ (where n is 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷.

R¹ and R² independently represent a hydrogen atom, halogen, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl or a C₁-alkyl group, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, NR⁶R⁷, OR⁶, S(O)_nR⁶ (where n is 0, 1 or 2);

or

R¹ and R² together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁶ and itself optionally substituted by one or more C₁-C₃ alkyl or halogen;

R³ represents C₃-C₇ cycloalkyl or C₁-alkyl which may be optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

R⁴ and R⁵ independently represent hydrogen, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

or

R⁴ and R⁵ together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n (where n = 0, 1 or 2), NR⁸, and itself optionally substituted by halogen or C₁-alkyl;

R⁶ and R⁷ independently represents a hydrogen atom or C₁-C₆ alkyl;

R⁸ is hydrogen, C₁-C₄ alkyl, -CO-C₁-C₄ alkyl, CO₂C₁-C₄ alkyl or CONR⁶C₁-C₄ alkyl;

R⁹ represents aryl, heteroaryl, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, aryl, heteroaryl OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

R¹⁰ and R¹¹ independently represent aryl or heteroaryl, hydrogen, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, aryl, heteroaryl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

or

R¹⁰ and R¹¹ together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n (where n = 0, 1 or 2), NR⁸, and itself optionally substituted by halogen or C₁-C₃ alkyl.

Examples of aryl include phenyl and naphthyl.

Heteroaryl is defined as a 5-7 member aromatic ring or can be 6,6- or 6,5-fused bicyclic ring optionally containing one or more heteroatoms selected from N, S and O. The bicyclic ring may be linked through carbon or nitrogen and may be attached through the 5 or 6 membered ring and can be fully or partially saturated.

Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone and 1,2-methylenedioxy benzene.

Aryl or heteroaryl groups can be optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, OH, SH, nitro, CO₂R⁶, SO₂R⁹, OR⁹, SR⁹, SOR⁹, SO₂NR¹⁰R¹¹, CONR¹⁰R¹¹, NR¹⁰R¹¹, NHSO₂R⁹, NR⁹SO₂R⁹, NR⁶CO₂R⁶, NHCOR⁹, NR⁹COR⁹, aryl, heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl or C₁-alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶, NR⁶R⁷, S(O)_nR⁶ (where n is 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷. Substituents can be present at any suitable position, including appropriate substituents on nitrogen atoms.

The group A is a six membered heterocyclic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicyclic containing one or more O, N, S atoms. Examples of suitable rings include pyridine, pyrimidine, pyrazine, pyridazine, indole, quinoline, isoquinoline, benzimidazole, benzthiazole, benzofuran, benzoxazole, benzthiophene, 5 phthalazine and quinazoline.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched.

10 Heterocyclic rings as defined for R⁴, R⁵ and R¹⁰ and R¹¹ means saturated heterocycles, examples include morpholine, azetidine, pyrrolidine, piperidine and piperazine. Substitents can be present on carbon and appropriate nitrogen atoms of said rings.

15 Preferably X is trifluoromethyl, nitro, cyano or halogen. More preferably X is trifluoromethyl, nitro, cyano, chloro or fluoro, even more preferably X is trifluoromethyl, chloro or fluoro. Most preferably X is trifluoromethyl or chloro.

Preferably Y is hydrogen, halogen or C₁₋₃alkyl. More preferably Y is hydrogen, fluoro or methyl. Most preferably Y is hydrogen.

20 25 Preferably Z is phenyl, pyridinyl, pyrimidyl, naphthyl, quinolyl, benzo[b]thienyl or benzofuranyl each optionally substituted as defined above, more preferably phenyl optionally substituted as defined above. Preferred substituents for all Z groups include those substituents exemplified herein, in particular halogen, C₁₋₃alkyl, cyano, SO₂R⁹, OR⁹, SR⁹, CO₂R⁶, NHSO₂R⁹, NR⁹SO₂R⁹ and SO₂NR¹⁰R¹¹.

More preferably when Z is phenyl it is optionally substituted by one to three, preferably one or two, substituents selected from SEt, SO₂Me, SO₂Et, chloro, fluoro, cyano, methoxy, propoxy, CO₂H, methyl, ethyl, propyl, butyl, amino, hydroxyl, NHCONHET, 30 NHCONHMe, NHCONHPr, NHCONH-cyclopropyl, CONH₂, SO₂NH₂, OCF₃, COMe, CO₂Me, nitro, phenyl, SCF₃, 1-pyrrolidinylsulphonyl, dimethylaminosulphonyl, ((phenylmethyl)amino)sulphonyl, [(2,2,2-trifluoroethyl)]amino]sulphonyl, [(5-methyl-2-thiazolyl)amino]sulphonyl, (phenylamino)sulphonyl,(diethylamino)sulphonyl, (cyclopropylamino)sulphonyl, aminosulphonyl, (methylamino)sulphonyl, (4-methyl-1-piperazinyl)sulphonyl, NHCO₂Me, (dimethylamino)sulphonyl, 4-morpholinylsulphonyl, 1-azetidinylsulphonyl, and 1-pyrrolidinylcarbonyl.

More preferably when Z is pyridyl it is optionally substituted by one or two groups selected from SO₂NH₂, methyl, amino, chloro and NMeSO₂Me,.

More preferably when Z is pyrimidine it is optionally substituted by one or two groups selected from amino, methyl, morpholinyl, dimethylamino, methylamino, benzylamino, piperidine, NMeSO₂Me, (methylsulphonul)(benzyl)amino, (ethylsulphonul)(benzyl)amino, acetyl(phenylmethyl)amino, 5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl, 1,1-dioxido-2-isothiazolidinyl, 3-hydroxy-1-azetidinyl, 4-methyl-1-piperazinyl, 1-pyrrolidinyl and NHSO₂NMe₂.

When Z is naphthyl it is preferably substituted with methoxy.

When Z is quinolyl, benzo[b]thienyl or benzofuranyl these groups are preferably unsubstituted.

Preferably R¹ and R² are independently hydrogen or C₁₋₃ alkyl. More preferably both R¹ and R² are hydrogen or one is hydrogen and the other is methyl or ethyl or both are methyl. Most preferably both R¹ and R² are hydrogen.

Preferred compounds of the invention include those exemplified herein both in free base form as well as pharmaceutically acceptable salts and solvates thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

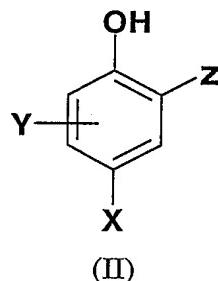
The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press

(1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

Compounds of formula (I) can be prepared by reaction of a compound of formula (II):

5



in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, with
10 a compound of formula (III):



Where R¹ and R² are as defined in formula (I) or are protected derivatives thereof, R¹² is H
15 or C₁-C₁₀ alkyl group and L is a leaving group, and optionally thereafter in any order:

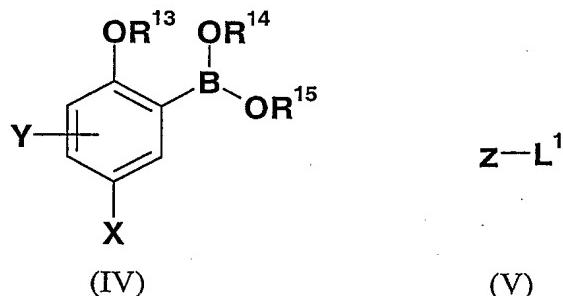
- removing any protecting group
- hydrolysing the ester group R¹² to the corresponding acid
- oxidation of sulphides to sulfoxides or sulphones
- forming a pharmaceutically acceptable salt.

20

The reaction can be carried out in a suitable solvent such as DMF using a base such as potassium carbonate or the like. Suitable groups R¹² include C₁₋₆ alkyl groups such as methyl, ethyl or tert-butyl. Suitable L is a leaving group such as halo, in particular chlorine or bromine. L may also be hydroxy so that a Mitsunobu reaction may be
25 performed with compound (II) using for example triphenylphosphine and diethyl azodicarboxylate.

Hydrolysis of the ester group R¹² can be carried out using routine procedures, for example treatment of methyl and ethyl esters with aqueous sodium hydroxide, and treatment of
30 tert-butyl esters with acids such as trifluoroacetic acid.

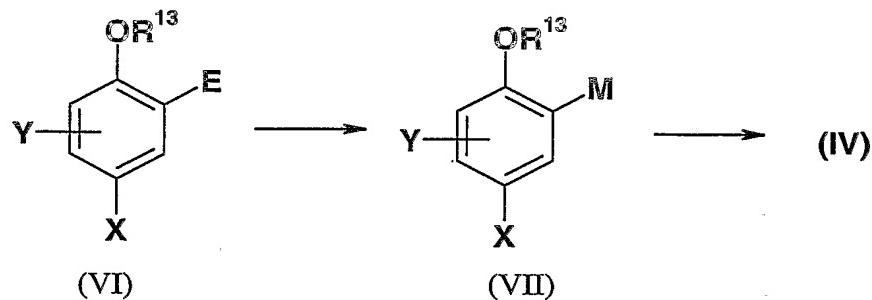
Compounds of formula (II) can be prepared by reaction of a compound of formula (IV) with a compound of formula (V) via a Suzuki coupling reaction followed by deprotection of group R¹³ when R¹³ is not equal to H :



- 5 in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, R¹³ is H or a suitable protecting group, for example benzyl, L¹ is iodide, bromide, chloride or triflate and R¹⁴ and R¹⁵ are H or C₁-C₆ alkyl groups or R¹⁴ and R¹⁵ together can form a 5 or 6 membered ring optionally substituted by one or more C₁-C₃ alkyl.

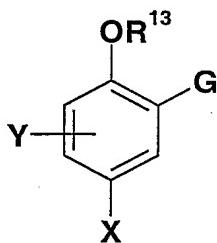
10 The reaction can be carried out in a suitable solvent such as dioxane using a palladium catalyst such as [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium and a base such as cesium fluoride, preferably at elevated temperatures.

Compounds of formula (IV) can be prepared from a compound of formula (VI) by formation of an organometallic (VII) followed by reaction with a borate ester, as outlined in Scheme I.

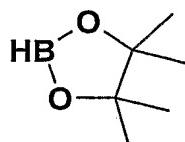


Scheme I

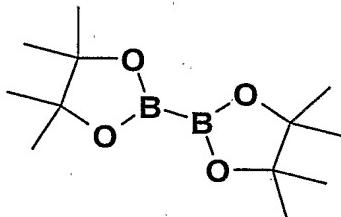
Compounds of formula (IV) may also be prepared by a palladium catalysed coupling of compounds of formula (VIII) with a suitable boronic ester, for example (IX) or (X).



(VIII)



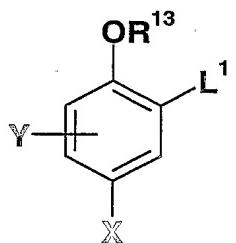
(IX)



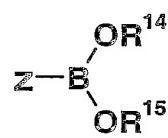
(X)

- 5 in which X, Y and R¹³ are as defined above and G is halogen or triflate

Compounds of formula (II) may also be prepared by reaction of a compound of formula (XI) with a compound of formula (XII) using Suzuki coupling methodology.



(XI)

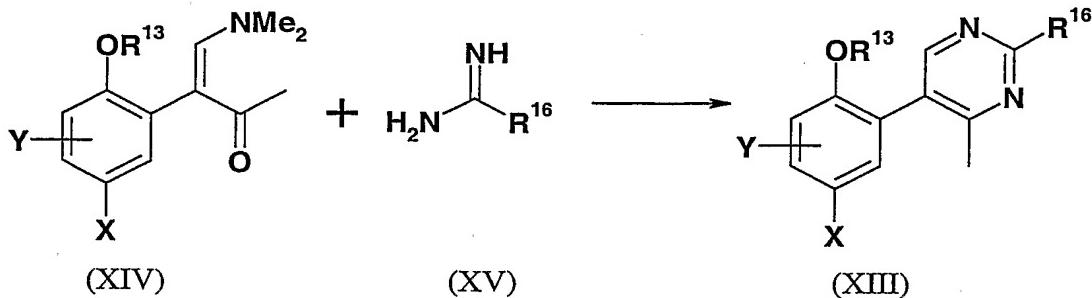


(XII)

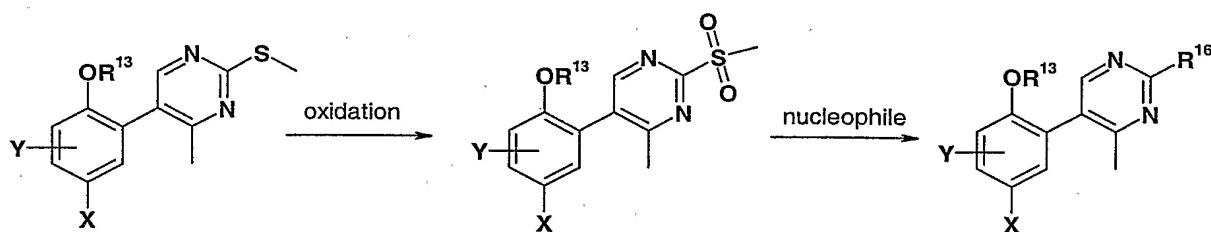
- in which X, Y, Z, R¹³, L¹, R¹⁴ and R¹⁵ are as defined above and compounds of formula (XI) and (XII) can be made using the same methodology as above.

- 15 Compounds of formula (II), where Z=heteroaryl may also be prepared by ring synthesis, for example a compound of formula (XIII) may be formed by reaction of a compound of formula (XIV) with a compound of formula (XV).

X, Y and R¹³ are as defined above and R¹⁶ is as defined as a substituent on Z as defined in formula (I) or are protected derivatives thereof. The reaction can be carried out in a solvent such as ethanol under reflux, and a base such as sodium ethoxide can be used if compound of formula (XV) is a salt

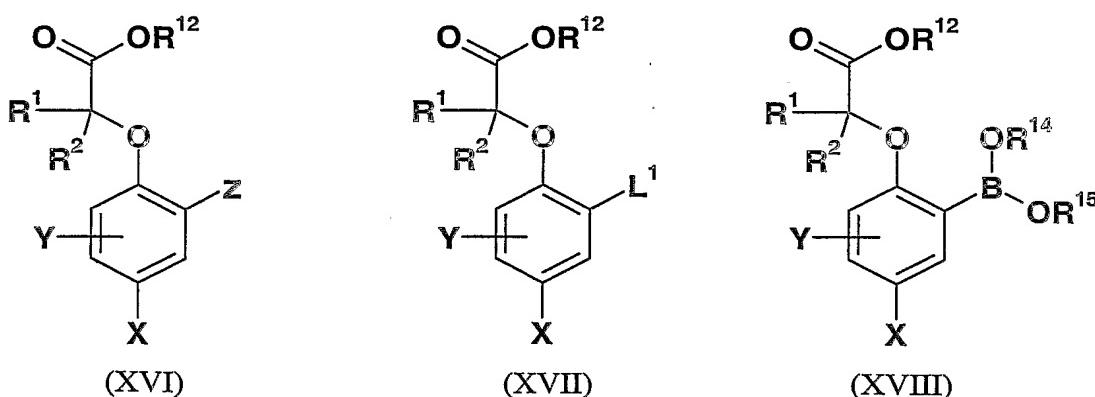


When R¹⁶ is a group S-alkyl, this may be further elaborated by oxidation to the sulfoxide or sulphone using an oxidizing agent such as mcpba in DCM at RT. This may then be displaced with an appropriate nucleophile as defined for Z in formula 1. Scheme 2;



Scheme 2

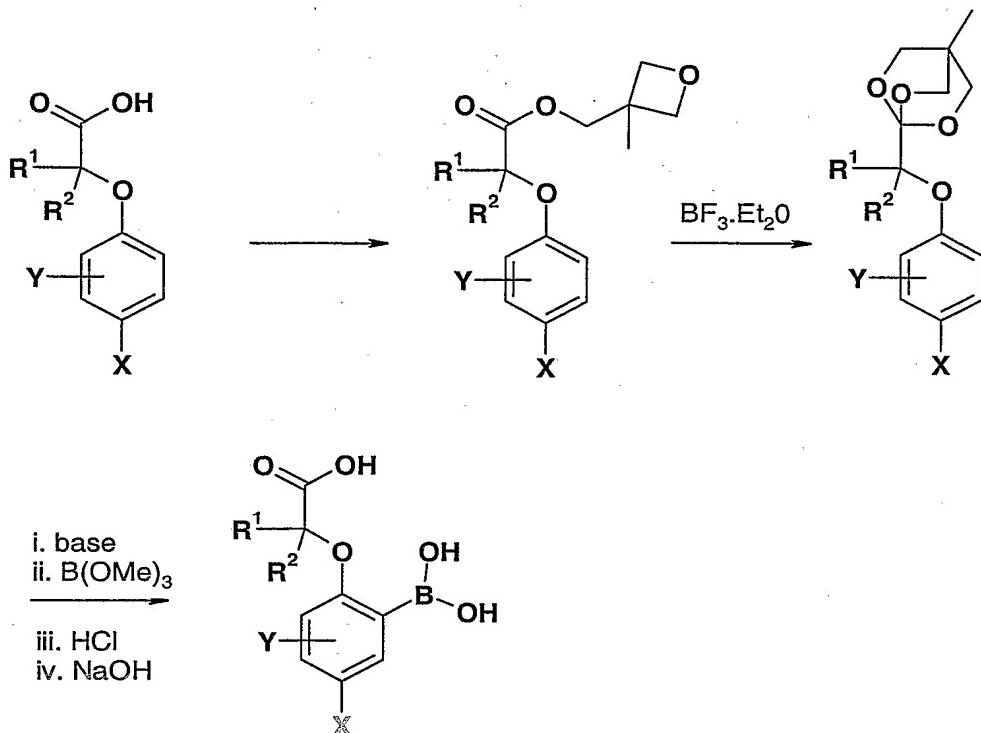
The sequence of the steps above may be changed, for example a compound of formula (XVI) may be formed by the reaction of a compound of formula (XVII) with a compound of formula (XII) using a Suzuki coupling.



Compounds of formula (I) may also be prepared by reaction of a compound of formula (XVIII) in which X, Y, R¹, R², R¹², R¹⁴ and R¹⁵ are as defined above with a compound of formula (V) using Suzuki coupling method as defined above.

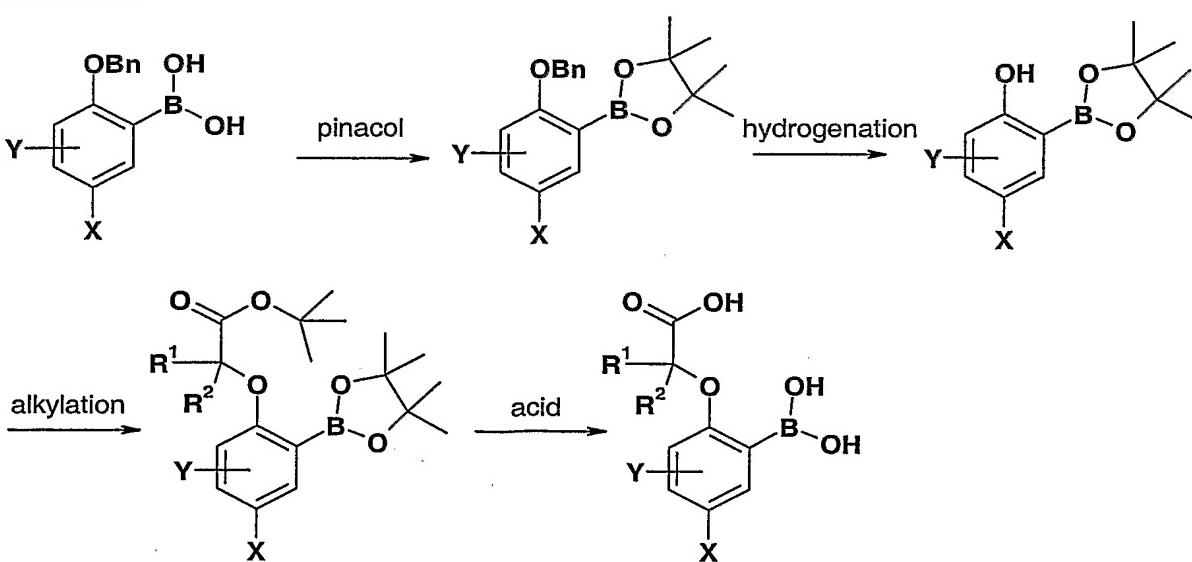
A compound of formula (XVIII) may be prepared by method A or B

25 Method A



The acid was first converted to the acid chloride, using for example oxalylchloride in DCM at RT, then reacted with 3-methyl-3-oxetanemethanol in the presence of a base such as triethylamine to give the ester. The oxetane ester is the rearranged to the OBO ester using boron trifluoride diethyletherate in DCM at -78°C to RT. Deprotonation with a base such as sec-butyl lithium at low temperature followed by quenching with trimethylborate gave the protected diacid which was then deprotected using HCl then sodium hydroxide

Method B



A compound of formula (IV) where R¹³ = Bn and R¹⁴ and R¹⁵ = H and pinacol can bestirred at RT in a suitable solvent such as diethylether to give the boronate ester. The benzyl group may be removed by hydrogenation at RT using palladium on carbon as catalyst then alkylated with a compound of formula (III) using a base or mitsunobu conditions.

- 5 Treatment with acid such as HCl or trifluoroacetic acid then removes the protecting groups.

In a further aspect, the present invention provides the use of a compound of formula (I), a prodrug, pharmaceutically acceptable salt or solvate thereof for use in therapy.

10 The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD₂ and its metabolites. Examples of such 15 conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness));

20 chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofulous 25 rhinitis, perennial allergic rhinitis, seasonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

30 (2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

35 (3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas,

vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areata corneal ulcer and vernal conjunctivitis;

5 (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

10 (5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal disorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

15

20 (6) **(other tissues and systemic disease)** atherosclerosis, acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs hepatitis (alcoholic, steatohepatitis and chronic viral), glomerulonephritis, renal impairment, chronic renal failure and other organs

25

30 (7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

35 (8) Diseases associated with raised levels of PGD₂ or its metabolites.

(1) (respiratory tract) - obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness ; chronic obstructive pulmonary disease (COPD) ; bronchitis , including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and 10 vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polypsis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

(2) (bone and joints) arthritides associated with or including osteoarthritis/osteoarthritis, both primary and secondary to e.g. congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial

Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies.

- (3) (skin) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.
- (4) (eyes) blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmritis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial.
- (5) (gastrointestinal tract) glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema).
- (6) (abdominal) hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic.
- (7) (genitourinary) nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female).
- (8) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

- (9) (CNS) Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoïdosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes.
- (10) Other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome.
- (11) Other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes.
- (12) (Cardiovascular); atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (e.g. syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins.
- (13) (Oncology) treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma ; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.
- (14) Diseases associated with raised levels of PGD₂ or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma,
5 rhinitis and other diseases in which raised levels of PGD₂ or its metabolites. It is preferred
that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or
a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the
10 manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or
a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the
manufacture of a medicament for use in therapy in combination with drugs used to treat
15 asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and
oral leukotriene receptor antagonists).

The invention further relates to combination therapies wherein a compound of formula (1)
or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a
20 pharmaceutical composition or formulation comprising a compound of formula (1) is
administered concurrently or sequentially or as a combined preparation with another
therapeutic agent or agents, for the treatment of one or more of the conditions listed .

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis,
25 inflammatory bowel disease, COPD, asthma and allergic rhinitis the compounds of the
invention may be combined with agents such as tumour necrosis factor alpha (TNF-α)
inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and
adalimumab) and TNF receptor immunoglobulin molecules (such as Enbrel); non-selective
cyclo-oxygenase (COX)-1 / COX-2 inhibitors whether applied topically or systemically
30 (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen,
ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac,
azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2
inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarcoxib, parecoxib
and etoricoxib); glucocorticosteroids (whether administered by topical, oral, intramuscular,
35 intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-
penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the
invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO)

inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonist for leukotrienes (LT)B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention together with a phosphodiesterase (PDE) inhibitor such as the methylxanthanines including theophylline and aminophylline; and selective PDE isoenzyme inhibitors including PDE4 inhibitors and inhibitors of the isoform PDE4D, and inhibitors of PDE5.

The present invention still further relates to the combination of a compound of the invention together with histamine type 1 receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, and mizolastine applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention together with a gastroprotective histamine type 2 receptor antagonist.

The present invention still further relates to the combination of a compound of the invention with antagonists of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention together with an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride, and ethynorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

5

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol .

10

The present invention still further relates to the combination of a compound of the invention together with a chromone, including sodium cromoglycate and nedocromil sodium.

15

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

20

The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and mometasone furoate.

25

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

30

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

35

The present invention still further relates to the combination of a compound of

the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or inhibitors, including agents which act on cytokine signalling pathways.

- 5 The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

The present invention still further relates to the combination of a compound of the

- 10 invention together with other systemic or topically-applied anti-inflammatory agents including thalidomide and derivatives, retinoids, dithranol, and calcipotriol.

The present invention still further relates to the combination of a compound of the invention together with an antibacterial agent including penicillin derivatives,

- 15 tetracyclines, macrolides, beta-lactams, flouroquinolones, and inhaled aminoglycosides; and antiviral agents including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir; amantadine, rimantadine; ribavirin; zanamavir and oseltamavir; protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir; nucleoside reverse transcriptase inhibitors such as didanosine, lamivudine, stavudine, zalcitabine, zidovudine; non-nucleoside reverse 20 transcriptase inhibitors such as nevirapine, efavirenz.

The present invention still further relates to the combination of a compound of the invention together with cardiovascular agents such as calcium channel blockers, beta-

- 25 adrenoceptor blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor antagonists; lipid lowering agents such as statins, and fibrates; modulators of blood cell morphology such as pentoxyfylline; thrombolytics, and anticoagulants including platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the

- 30 invention together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegiline and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, 35 tacrine, COX-2 inhibitors, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention together with agents for the treatment of acute and chronic pain, including centrally and peripherally-acting analgesics such as opioid analogues and derivatives,

carbamazepine, phenytoin, sodium valproate, amitryptyline and other antidepressant agents, and non-steroidal anti-inflammatory agents.

The present invention still further relates to the combination of a compound of the invention together with parenterally or topically-applied local anaesthetic agents such as lignocaine.

The present invention still further relates to the combination of a compound of the invention together with (i) tryptase inhibitors; (ii) platelet activating factor (PAF) antagonists; (iii) interleukin converting enzyme (ICE) inhibitors; (iv) IMPDH inhibitors; (v) adhesion molecule inhibitors including VLA-4 antagonists; (vi) cathepsins; (vii) MAP kinase inhibitors; (viii) glucose-6 phosphate dehydrogenase inhibitors; (ix) kinin-B₁. - and B₂. -receptor antagonists; (x) anti-gout agents, e.g., colchicine; (xi) xanthine oxidase inhibitors, e.g., allopurinol; (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzboromarone; (xiii) growth hormone secretagogues; (xiv) transforming growth factor (TGF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) Tachykinin NK₁. and NK₃. receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892; (xxi) TNF α converting enzyme inhibitors (TACE); (xxii) induced nitric oxide synthase inhibitors (iNOS) or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists) (xxiv) inhibitors of P38

The compounds of the present invention may also be used in combination with anti-osteoporosis agents including hormonal agents such as raloxifene, and biphosphonates such as alendronate.

The compounds of the invention may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAIDs) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics, and intra-articular therapies such as corticosteroids and hyaluronic acid derivatives, and nutritional supplements such as glucosamine.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin,

5 cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

10 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors 15 of 5 α -reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody 20 trastuzumab and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase

inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for

25 example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial

30 growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, compounds such as those disclosed in International Patent Applications

WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

- (vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;
- 5 (vii) antisense therapies, for example those which are directed to the targets listed above,
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to
- 10 chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as
- 15 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

- 5 For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

10 The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, 15 still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, . . . of active ingredient, all percentages by weight being based on total composition.

20 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25 The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

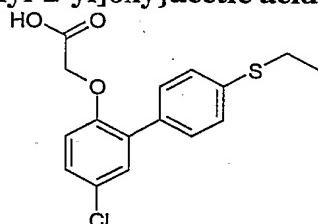
- 30 The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
- (i) when given, ¹H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
- 35 (ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - (M+H)⁺;
- (iii) the title compounds of the examples and methods were named using the ACD/name and ACD/name batch (version 6.0) from Advanced Chemical Development Inc, Canada;
- (iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry,

NovaPak or Ex-Terra reverse phase silica column;

(v) solvents were dried with MgSO₄ or Na₂SO₄

(vi) the following abbreviations are used:

5	EtOAc	Ethylacetate
	DCM	Dichloromethane
	NMP	N-methylpyrrolidine
	DMF	N,N-dimethylformamide
	THF	tetrahydrofuran
10	mcpba	3-chloroperoxybenzoic acid (Aldrich 77% max)
	Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
	RT	room temperature

Example 1**{[5-Chloro-4'-(ethylthio)biphenyl-2-yl]oxy}acetic acid**

5 (i) tert-Butyl (2-bromo-4-chlorophenoxy)acetate

tert-Butyl bromoacetate (2.6ml) was added to a stirred mixture of 4-bromo-2-chlorophenol (3g) and potassium carbonate (6.2g) in DMF (40ml) at RT. After 16h the reaction was partitioned between diethylether and water, the organics separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 4% EtOAc/iso-hexane. Yield 4.05g

¹H NMR CDCl₃: δ 7.55 (1H, d) ; 7.21 (1H, dd) ; 6.72 (1H, d) ; 4.57 (2H, s) ; 1.48 (9H, s)

(ii) tert-Butyl {[5-chloro-4'-(ethylthio)biphenyl-2-yl]oxy}acetate

15 A mixture of the product from step (i) (2g), 4-(ethylthio)phenylboronic acid (1.5g), cesium fluoride (2g) and Pd(dppf)Cl₂ (0.2g) in dioxane (40ml) was heated under reflux for 3h. After cooling the mixture was partitioned between diethylether and water. The organics were separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 5% EtOAc/iso-hexane. Yield 0.92g

20 MS: APCI (+ve): 379/381 (M+1)

(iii) {[5-Chloro-4'-(ethylthio)biphenyl-2-yl]oxy}acetic acid

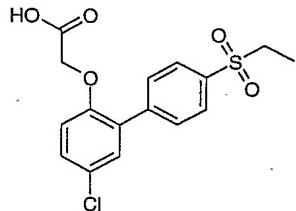
The title compound was prepared by stirring a mixture of the product from step (ii) (0.3g) and trifluoroacetic acid (4ml) in DCM (10ml) at RT for 5h. The solvent was evaporated under reduced pressure, the residue triturated with diethylether then purified by reverse phase HPLC. Yield 0.106g

¹H NMR DMSO-d6: δ 13.07 (1H, s) ; 7.54 (2H, d) ; 7.35-7.33 (4H, m) ; 7.02 (1H, d) ; 4.74

30 (2H, s) ; 3.02 (2H, q) ; 1.27 (3H, t)

MS: APCI (-ve): 321/3 (M-1)

Example 2**{[5-Chloro-4'-(ethylsulfonyl)biphenyl-2-yl]oxy}acetic acid**



(i) tert-Butyl {[5-chloro-4'-(ethylsulfonyl)biphenyl-2-yl]oxy}acetate

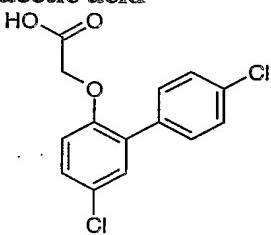
Mcpba (1.2g) was added to a stirred solution of the product from example 1 step (ii) (0.6g) in DCM (10ml) at RT. After 4h, the mixture was partitioned between DCM and aqueous sodium metabisulphite solution, the organics separated, washed with aqueous sodium hydrogencarbonate solution, water, dried and evaporated under reduced pressure. Yield 0.65g

(ii) {[5-Chloro-4'-(ethylsulfonyl)biphenyl-2-yl]oxy}acetic acid

The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.226g

¹H NMR DMSO-d6: δ 13.14 (1H, s) ; 7.92 (2H, d) ; 7.87 (2H, d) ; 7.45-7.42 (2H, m) ; 7.10 (1H, d) ; 4.79 (2H, s) ; 3.35 (2H, q) ; 1.15 (3H, t)

MS: APCI (-ve): 353/5 (M-1)

Example 3**[(4',5-Dichlorobiphenyl-2-yl)oxy]acetic acid**

(i) tert-Butyl [(4',5-dichlorobiphenyl-2-yl)oxy]acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 1 step (i) and 4-chlorophenylboronic acid. Yield 0.63g

¹H NMR CDCl₃: δ 7.54-7.22 (6H, m) ; 6.76 (1H, dd) ; 4.48 (2H, s) ; 1.47 (9H, s)

25

(ii) [(4',5-Dichlorobiphenyl-2-yl)oxy]acetic acid

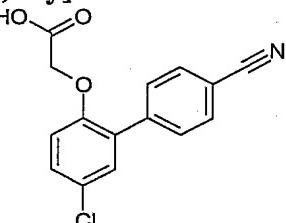
The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.224g

¹H NMR DMSO-d₆: δ 13.00 (1H, s) ; 7.61 (2H, d) ; 7.48 (2H, d) ; 7.41-7.36 (2H, m) ; 7.05 (1H, d) ; 4.75 (2H, s)

MS: APCI (-ve): 295/7 (M-1)

5 **Example 4**

[(5-Chloro-4'-cyanobiphenyl-2-yl)oxy]acetic acid



(i) tert-Butyl [(5-chloro-4'-cyanobiphenyl-2-yl)oxy]acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 1 step (i) and 4-cyanophenylboronic acid. Yield 0.524g

¹H NMR CDCl₃: δ 7.70 (4H, s) ; 7.32-7.26 (2H, m) ; 6.79 (1H, d) ; 4.51 (2H, s) ; 1.48 (9H, s)

15 (ii) [(5-Chloro-4'-cyanobiphenyl-2-yl)oxy]acetic acid

The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.109g

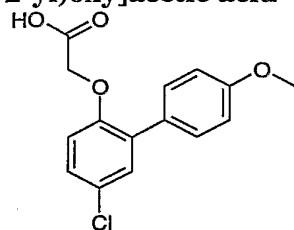
¹H NMR DMSO-d₆: δ 13.14 (1H, s) ; 7.90 (2H, d) ; 7.80 (2H, d) ; 7.45-7.41 (2H, m) ; 7.10

20 (1H, d) ; 4.78 (2H, s)

MS: APCI (-ve): 286/8 (M-1)

Example 5

[(5-Chloro-4'-methoxybiphenyl-2-yl)oxy]acetic acid



(i) tert-Butyl [(5-chloro-4'-methoxybiphenyl-2-yl)oxy]acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 1 step (i) and 4-methoxyphenylboronic acid. Yield 0.610g

¹H NMR CDCl₃: δ 7.54 (2H, d) ; 7.31-7.18 (2H, m) ; 6.96 (2H, d) ; 6.76 (1H, d) ; 4.46 (2H, s) ; 3.84 (3H, s) ; 1.46 (9H, s)

5 (ii) [(5-Chloro-4'-methoxybiphenyl-2-yl)oxy]acetic acid

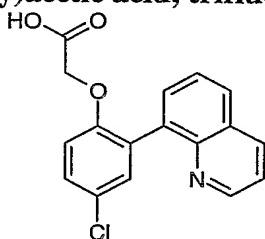
The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.119g

¹H NMR DMSO-d6: δ 13.08 (1H, s) ; 7.53 (2H, d) ; 7.32-7.29 (2H, m) ; 7.01-6.96 (3H, m) ; 4.72 (2H, s) ; 3.79 (3H, s)

10 MS: APCI (-ve): 291/3 (M-1)

Example 6

(4-Chloro-2-quinolin-8-ylphenoxy)acetic acid, trifluoroacetic acid salt



15

(i) tert-Butyl (4-chloro-2-quinolin-8-ylphenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 1 step (i) and 8-quinoline boronic acid. Yield 0.356g

20 ¹H NMR CDCl₃: δ 8.90-8.88 (1H, m) ; 8.18 (1H, d) ; 7.85 (1H, d) ; 7.76 (1H, d) ; 7.60 (1H, t) ; 7.40-7.30 (3H, m) ; 6.87 (1H, d) ; 4.37 (2H, s) ; 1.37 (9H, s)

(ii) (4-Chloro-2-quinolin-8-ylphenoxy)acetic acid, trifluoroacetic acid salt

25 The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.25g

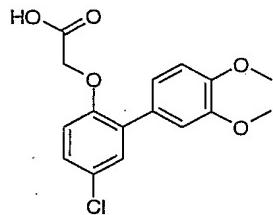
¹H NMR DMSO-d6: δ 8.91-8.89 (1H, m) ; 8.62 (1H, d) ; 8.12 (1H, d) ; 7.85-7.67 (3H, m) ; 7.46 (1H, dd) ; 7.38 (1H, d) ; 7.09 (1H, d) ; 4.61 (2H, s)

MS: APCI (-ve): 312/4 (M-1)

30

Example 7

[(5-Chloro-3',4'-dimethoxybiphenyl-2-yl)oxy]acetic acid



(i) tert-Butyl [(5-chloro-3',4'-dimethoxybiphenyl-2-yl)oxy]acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 1 step (i) and 3,4-dimethoxyphenylboronic acid. Yield 0.86g

5

¹H NMR CDCl₃: δ 7.33-7.12 (4H, m); 6.93 (1H, d); 6.79 (1H, d); 4.46 (2H, s); 3.93 (3H, s); 3.92 (3H, s); 1.46 (9H, s)

(ii) [(5-Chloro-3',4'-dimethoxybiphenyl-2-yl)oxy]acetic acid

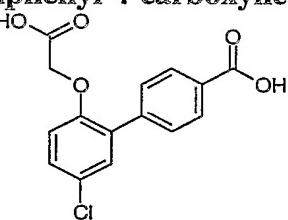
10 The title compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 0.32g

¹H NMR DMSO-d6: δ 13.08 (1H, s); 7.36-7.27 (3H, m); 7.12-6.98 (3H, m); 4.74 (2H, s); 3.78 (6H, 2xs)

15 MS: APCI (-ve): 321/3 (M-1)

Example 8

2'-(Carboxymethoxy)-5'-chlorobiphenyl-4-carboxylic acid



20 The title compound was prepared by the method of example 1 step (ii) and step (iii) using the product from example 1 step (i) and 4-carboxyphenylboronic acid. Yield 0.035g

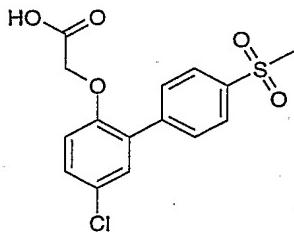
¹H NMR DMSO-d6: δ 7.98-7.38 (6H, m); 7.08-7.05 (1H, m); 4.75 (2H, s)

MS: APCI (-ve): 305 (M-1)

25

Example 9

{[5-Chloro-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid



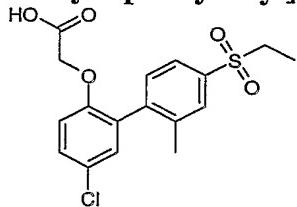
The title compound was prepared by the method of example 1 step (ii) and example 2 using the product from example 1 step (i) and 4-(methylthio)benzeneboronic acid. Yield 0.1g

5

¹H NMR DMSO-d₆: δ 7.97-7.08 (7H, m); 4.78 (2H, s); 3.31 (3H, bs)
MS: APCI (-ve): 339 (M-1)

Example 10

10 {[5-Chloro-4'-(ethylsulfonyl)-2'-methylbiphenyl-2-yl]oxy}acetic acid



(i) 4-Bromo-3-methylphenyl ethyl sulfide

Bromine (2.2ml) was added to a solution of 1-(ethylthio)-3-methylbenzene (6.6g) in acetic acid (20ml) at 0°C. The mixture was stirred at RT for 2h then the solvent removed under reduced pressure. The residue was purified by chromatography on silica eluting with DCM. Yield 6.6g

MS: APCI (+ve): 247/9 (M+1)

(ii) 2-[4-(Ethylthio)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

20 A mixture of the product from step (i) (6.6g), 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (1.94ml), triethylamine (2.4ml), palladium acetate (0.06g) and 2-(dicyclohexylphosphino)biphenyl (0.3g) in dioxane (20ml) was heated at 85°C for 2h. The mixture was quenched with aqueous ammonium chloride solution, extracted with diethylether, the organics dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 50% isohexane/DCM. Yield 0.7g

25 ¹H NMR CDCl₃: δ 7.66 (1H, d); 7.08-7.05 (2H, m); 2.94-2.92 (2H, q); 2.5 (3H, s); 1.43-1.27 (15H, m)

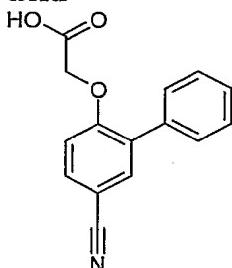
30 (iii) {[5-Chloro-4'-(ethylsulfonyl)-2'-methylbiphenyl-2-yl]oxy}acetic acid

The title compound was prepared by the method of example 1 step (ii) and example 2 using the product from step (ii) and the product from example 1 step (i). Yield 0.035g

¹H NMR DMSO-d₆: δ 7.79-6.99 (6H, m) ; 4.67 (2H, s) ; 3.35 (2H, q) ; 2.23 (3H, s) ; 1.15 (3H, t)
 5 MS: APCI (-ve): 367 (M-1)

Example 11

[(5-Cyanobiphenyl-2-yl)oxy]acetic acid



10

The title compound was prepared by the method of example 1 using 3-bromo-4-hydroxybenzonitrile and phenylboronic acid. Yield 0.175g

¹H NMR DMSO-d₆: δ 13.18 (1H, s) ; 7.81-7.17 (8H, m) ; 4.87 (2H, s)
 15 MS: APCI (-ve): 252 (M-1)

Example 12

[(5-Nitrobiphenyl-2-yl)oxy]acetic acid

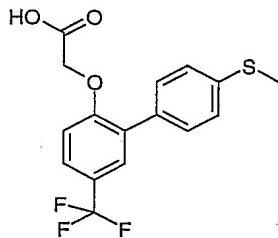


20 The title compound was prepared by the method of example 1 using 2-bromo-4-nitrophenol and phenylboronic acid. Yield 0.065g

¹H NMR DMSO-d₆: δ 13.26 (1H, s) ; 8.23 (1H, dd) ; 8.12 (1H, d) ; 7.63 (2H, d) ; 7.50-7.38 (3H, m) ; 7.25 (1H, d) ; 4.94 (2H, s)
 25 MS: APCI (-ve): 272 (M-1)

Example 13

{[4'-(Methylthio)-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid



(i) 2-Iodo-4-(trifluoromethyl)phenol

Sodium iodide (3.32g) then chloramine-T (5.91g) were added to a stirred solution of 4-trifluoromethylphenol (3.0g) in DMF (30ml) at 0°C. The mixture was warmed to RT, stirred for 1h, diluted with dilute hydrochloric acid then extracted with diethylether. The organic layer was washed with aqueous sodium thiosulphate solution, dried and the solvent removed under reduced pressure. Yield 5.25g

MS: APCI (-ve): 287 (M-1)

10

(ii) {[4'-(Methylthio)-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid

The title compound was prepared by the method of example 1 using the product from step (i) and 4-(methylthio)benzeneboronic acid. Yield 0.13g

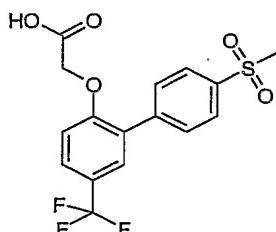
15

¹H NMR DMSO-d6: δ 13.16 (1H, s) ; 7.68-7.18 (7H, m) ; 4.85 (2H, s) ; 2.51 (3H, s)

MS: APCI (-ve): 341 (M-1)

Example 14

{[4'-(Methylsulfonyl)-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid, ammonium salt



The title compound was prepared by the methods of example 1 and 2 using the product from example 13 step (i) and 4-(methylthio)benzeneboronic acid. Yield 0.14g

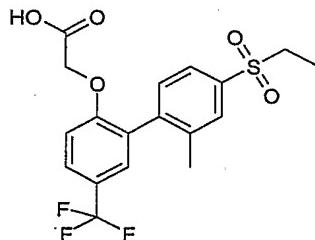
25

¹H NMR DMSO-d6: δ 13.21 (1H, s) ; 8.00-7.69 (6H, m) ; 7.27 (1H, d) ; 4.89 (2H, s) ; 3.27 (3H, s)

MS: APCI (-ve): 373 (M-1)

Example 15

{[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid



The title compound was prepared by the methods of example 1 and 2 using the product from example 13 step (i) and the product from example 10 step (ii). Yield 0.055g

5 ¹H NMR DMSO-d6: δ 7.80-7.12 (6H, m) ; 4.63 (2H, s) ; 3.39-3.29 (2H, q) ; 2.23 (3H, s) ;
1.18-1.11 (3H, t)
MS: APCI (-ve): 401 (M-1)

Example 16

10 (4-Chloro-2-pyrimidin-5-ylphenoxy)acetic acid, ammonium salt



(i) Benzyl 2-bromo-4-chlorophenyl ether

Benzyl bromide (13.1ml) was added to a stirred mixture of 2-bromo-4-chlorophenol (20.7g) and potassium carbonate (27.6g) in DMF (200ml). After 72h, the mixture was partitioned between diethylether and water, the organic layer washed with water, dried and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 2% EtOAc/isohexane. Yield 18.1g

15 ¹H NMR CDCl₃: δ 7.55 (1H, s) ; 7.46-7.18 (6H, m) ; 6.84 (1H, d) ; 5.14 (2H, s)

20

(ii) [2-(Benzylxy)-5-chlorophenyl]boronic acid

A solution of butyl lithium (1.6M in hexane) (50ml) was added dropwise to a stirred solution of the product from step (i) (23g) in diethylether (300ml) at -70°C. After 1h a further 18ml of butyl lithium was added, left for 0.75h, then trimethylborate (10ml) added and the mixture warmed to RT and left for 16h. 2M Hydrochloric acid (100ml) was added, stirred for 1h then the organic layer separated and extracted with aqueous sodium hydroxide solution. The basic layer was acidified with 2M hydrochloric acid solution, extracted with diethylether which was dried and evaporated under reduced pressure. The residue was triturated with iso-hexane and filtered. Yield 10.8g

¹H NMR CDCl₃: δ 7.82 (1H, d) ; 7.44-7.34 (6H, m) ; 6.90 (1H, d) ; 5.99 (2H, s) ; 5.12 (2H, s)

5 (iii) 5-[2-(Benzylxy)-5-chlorophenyl]pyrimidine

A mixture of the product from step (ii) (0.2g), 5-bromopyrimidine (0.16g), sodium carbonate (0.21g) and tetrakis(triphenylphosphine) palladium (0) (0.05g) in dioxane (6ml) was heated under reflux for 48h. The mixture was partitioned between EtOAc and water, the organics separated, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 20% EtOAc/iso hexane. Yield 0.283g.

10 MS: APCI (+ve): 297/9 (M+1)

15 (iv) 4-Chloro-2-pyrimidin-5-ylphenol

A mixture of the product from step (iii) (0.28g), 10% palladium on carbon (0.04g) in ethanol (20ml) was hydrogenated at 2Bar for 24h. After filtration the solvent was evaporated under reduced pressure. Yield 0.19g

20 MS: APCI (+ve): 207/9 (M+1)

25 (v) tert-Butyl (4-chloro-2-pyrimidin-5-ylphenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (i). Yield 0.216g

MS: APCI (+ve): 321/3 (M+1)

25 (vi) (4-Chloro-2-pyrimidin-5-ylphenoxy)acetic acid, ammonium salt

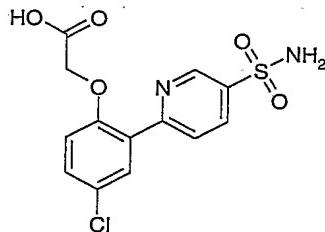
The title compound was prepared by the method of example 1 step (iii). Yield 0.033g

¹H NMR DMSO-d6: δ 9.15 (1H, s) ; 9.08 (2H, s) ; 7.57 (1H, d) ; 7.44 (1H, dd) ; 7.10 (1H, d) ; 4.67 (2H, s)

30 MS: APCI (+ve): 265/7(M+1)

Example 17

{2-[5-(Aminosulfonyl)pyridin-2-yl]-4-chlorophenoxy}acetic acid



The title compound was prepared by the method of example 16. Yield 0.022g

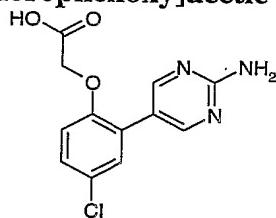
¹H NMR DMSO-d₆: δ 13.19 (1H, s) ; 9.05 (1H, s) ; 8.29 (1H, d) ; 8.21 (1H, d) ; 7.84 (1H,

5 d) ; 7.65 (2H, s) ; 7.49 (1H, dd) ; 7.16 (1H, d) ; 4.86 (2H, s)

MS: APCI (+ve): 343/5(M+1)

Example 18

[2-(2-Aminopyrimidin-5-yl)-4-chlorophenoxy]acetic acid, trifluoroacetate salt



10

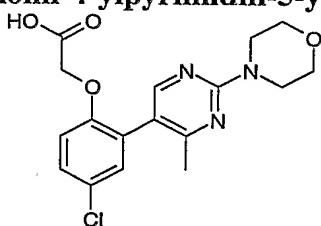
The title compound was prepared by the method of example 16. Yield 0.036g

¹H NMR DMSO-d₆: δ 8.56 (2H, s) ; 7.45 (1H, d) ; 7.33 (1H, dd) ; 7.05 (1H, d) ; 4.76 (2H, s)

15 MS: APCI (+ve): 280/2(M+1)

Example 19

[4-Chloro-2-(4-methyl-2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetic acid



20 (i) 2-[2-(Benzylxy)-5-chlorophenyl]-N-methoxy-N-methylacetamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.6g) was added to a solution of (2-benzylxy-5-chlorophenyl)-acetic acid (10.6g), N,O-dimethylhydroxylamine hydrochloride (4.4g), 1-hydroxybenzotriazole (6.9g) and N,N-diisopropylethylamine (20ml) in DMF (150ml) and the mixture stirred at RT for 16h, then partitioned between ethylacetate and water. The organics were washed with 2M hydrochloric acid, water, dried, and evaporated under reduced pressure. Yield 12.2g

MS: APCI (+ve): 320/2(M+1)

(ii) 1-[2-(BenzylOxy)-5-chlorophenyl]acetone

5 A solution of methylmagnesium chloride (3M in THF) (6ml) was added dropwise to a stirred solution of the product from step (i) (5.2g) in THF (150ml) at -70°C. After 1h the mixture was warmed to RT, stirred for 1h then quenched with aqueous ammonium chloride solution. The mixture was partitioned between diethylether and water, the organics separated, dried, and evaporated under reduced pressure. The residue was purified by
10 chromatography on silica eluting with 10% EtOAc/isohexane. Yield 2.22g

¹H NMR CDCl₃: δ 7.40-7.30 (5H, m) ; 7.26-7.12 (2H, m) ; 6.85 (1H, d) ; 5.03 (2H, s) ;
3.67 (2H, s) ; 2.12 (3H, s)

15 (iii) (3Z)-3-[2-(BenzylOxy)-5-chlorophenyl]-4-(dimethylamino)but-3-en-2-one
A mixture of the product from step (ii) (5.72g) and dimethylformamide dimethyl acetal (3.5ml) in toluene (50ml) were heated at 100°C for 12h. The solvent was evaporated under reduced pressure to give an oil, 6.37g.

20 MS: APCI (+ve): 330/2(M+1)

(iv) 5-[2-(BenzylOxy)-5-chlorophenyl]-4-methyl-2-(methylthio)pyrimidine

A solution of the product from step (iii) (4.3g) in ethanol (20ml) was added to a stirred mixture of sodium ethoxide (0.98g) and S-methylisothiouronium sulphate (2g) in ethanol
25 (30ml), and the mixture heated under reflux for 8h. A further 2g of S-methylisothiouronium sulphate and 1.18g of sodium ethoxide were added and heating continued for 16h. The mixture was cooled, partitioned between diethylether and water, the organics washed with water, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 3-5% EtOAc/iso hexane.
30 Yield 1.84g

MS: APCI (+ve): 357/9(M+1)

(v) 5-[2-(BenzylOxy)-5-chlorophenyl]-4-methyl-2-(methylsulfonyl)pyrimidine

35 The subtitle compound was prepared by the method of example 2 step (i). Yield 0.85g

MS: APCI (+ve): 389/91(M+1)

(vi) 4-Chloro-2-[4-methyl-2-(methylsulfonyl)pyrimidin-5-yl]phenol

The subtitle compound was prepared by the method of example 16 step (iv). Yield 0.5g

MS: APCI (+ve): 299/301(M+1)

- 5 (vii) tert-Butyl {4-chloro-2-[4-methyl-2-(methylsulfonyl)pyrimidin-5-yl]phenoxy}acetate

The subtitle compound was prepared by the method of example 1 step (i). Yield 0.65g

MS: APCI (+ve): 413(M+1)

10

- (viii) tert-Butyl [4-chloro-2-(4-methyl-2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetate

A solution of the product from step (vii) (0.15g) and morpholine (0.15ml) in dioxane (3ml) was heated at 90°C for 24h, cooled and the solvent evaporated under reduced pressure.

15

Product used crude.

MS: APCI (+ve): 420/422(M+1)

- (ix) [4-Chloro-2-(4-methyl-2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetic acid

The title compound was prepared by the method of example 1 step (iii). Yield 0.046g

20

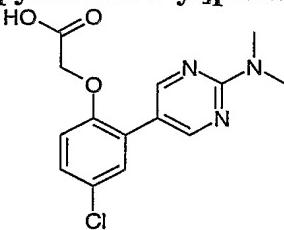
¹H NMR DMSO-d6: δ 8.12 (1H, s) ; 7.39 (1H, dd) ; 7.25 (1H, d) ; 7.00 (1H, d) ; 4.71 (2H, s) ; 3.73-3.67 (8H, m) ; 2.18 (3H, s)

MS: APCI (+ve): 364/6(M+1)

25

Example 20

{4-Chloro-2-[2-(dimethylamino)pyrimidin-5-yl]phenoxy}acetic acid



- (i) 5-[2-(Benzyl)oxy]-5-chlorophenyl]-2-chloropyrimidine

The subtitle compound was prepared by the method of example 1 step (ii) using the

30 product from example 16 step (ii) (3.2g) and 2-chloro-5-bromopyrimidine (2.59g). Yield 2.43g

MS: APCI (+ve): 331/3(M+1)

- (ii) 5-[2-(Benzyl)oxy]-5-chlorophenyl]-2-(propylthio)pyrimidine

Propanethiol (3.1ml) was added to a stirred suspension of sodium hydride (1.4g, 60% in oil) in DMF (30ml). After 1 hour a solution of the product from step (i) (2.4g) in DMF (10ml) was added. The reaction mixture was stirred at RT for 1 hour then partitioned between EtOAc and water. The organics were washed with water, brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 5% EtOAc/isohexane. Yield 1.87g

MS: APCI(+ve) 371 (M+1)

(iii) 5-[2-(Benzylxy)-5-chlorophenyl]-2-(propylsulfonyl)pyrimidine

The subtitle compound was prepared by the method of example 2 step (i) using the product from step (ii).

MS: APCI(+ve) 403 (M+1)

(iv) tert-Butyl {4-chloro-2-[2-(propylsulfonyl)pyrimidin-5-yl]phenoxy}acetate

The subtitle compound was prepared by the method of example 16 step (iv) and example 1 step (i) using the product from step (iii). Yield 1.04g

MS: APCI(+ve) 427 (M+1)

(v) {4-Chloro-2-[2-(dimethylamino)pyrimidin-5-yl]phenoxy}acetic acid

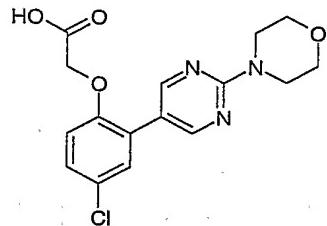
Dimethylamine hydrochloride (0.82g) was added to a stirred solution of the product from step (iv) (0.2g) and N,N-diisopropylethylamine (0.9ml) in NMP (5ml). The reaction mixture was heated at 90°C for 6h then diluted with EtOAc, washed with water, brine, dried and evaporated under reduced pressure. The residue was dissolved in DCM (10ml) then trifluoroacetic acid (10ml) added and stirred for 18h at RT. The reaction mixture was evaporated to dryness and the residue purified by reverse phase HPLC followed by trituration with methanol to give a white solid. Yield 0.035g

1H NMR DMSO-d6: δ8.60 (2H, s) ; 7.42 (1H, d) ; 7.32 (1H, dd) ; 7.05 (1H, d) ; 4.77 (2H, s) ; 3.16 (6H, s).

MS: APCI(-ve) 306 (M-1)

Example 21

[4-Chloro-2-(2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetic acid

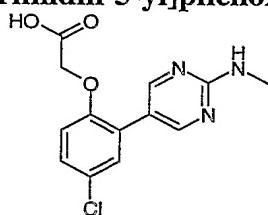


The title compound was prepared from the product of example 20 step (iv) and morpholine by the method of example 20 step (v).

- 5 ^1H NMR DMSO-d₆: δ 13.10 (1H, brs) ; 8.65 (2H, s) ; 7.45 (1H, d) ; 7.34 (1H, dd) ; 7.06
 (1H, d) ; 4.77 (2H, s) ; 3.75 (4H, m) ; 3.67 (4H, m)
 MS: APCI(-ve) 348 (M-1)

Example 22

- 10 **{4-Chloro-2-[2-(methylamino)pyrimidin-5-yl]phenoxy}acetic acid**

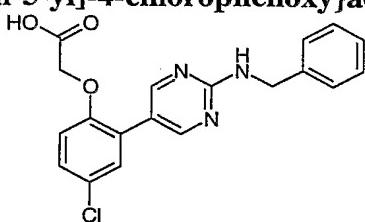


The title compound was prepared from the product of example 20 step (iv) and methylamine hydrochloride by the method of example 20 step (v).

- 15 ^1H NMR DMSO-d₆: δ 8.54 (2H, s) ; 7.42 (1H, d) ; 7.32 (1H, dd) ; 7.25 (1H, brs) ; 7.04 (1H, d) ; 4.76 (2H, s) ; 2.84 (3H, s)
 MS: APCI(-ve) 292 (M-1)

Example 23

- 20 **{2-[2-(Benzylamino)pyrimidin-5-yl]-4-chlorophenoxy}acetic acid**



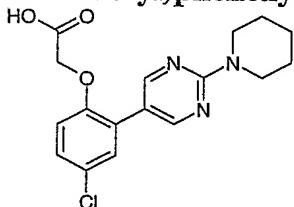
The title compound was prepared from the product of example 20 step (iv) and benzylamine by the method of example 20 step (v).

- 25 ^1H NMR DMSO-d₆: δ 13.09 (1H, brs) ; 8.54 (2H, s) ; 7.90 (1H, t) ; 7.42 (1H, d) ; 7.35-7.29 (5H, m) ; 7.22 (1H, m) ; 7.03 (1H, d) ; 4.76 (2H, s) ; 4.55 (2H, d)

MS: APCI(-ve) 368 (M-1)

Example 24

[4-Chloro-2-(2-piperidin-1-ylpyrimidin-5-yl)phenoxy]acetic acid



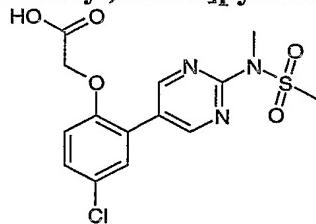
5

The title compound was prepared from the product of example 20 step (iv) and piperidine by the method of example 20 step (v).

1H NMR DMSO-d₆: δ13.10 (1H, brs) ; 8.59 (1H, d) ; 7.32 (1H, dd) ; 7.04 (1H, d) ; 4.77
10 (2H, s) ; 3.79 (4H, t) ; 1.65 (2H, m) ; 1.53 (4H, m)
MS: APCI(-ve) 346 (M-1)

Example 25

(4-Chloro-2-{2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}phenoxy)acetic acid



15

(i) N-(5-Bromopyrimidin-2-yl)-N-methylmethanesulfonamide
Sodium hydride (0.22g, 60% in oil) was added to a solution of (5-bromopyrimidin-2-yl)methylamine (0.85g) in DMF (10ml) at 0°C and stirred for 30min. Methanesulphonyl chloride (0.62g) was added dropwise, the mixture warmed to RT and stirred for a further 20 2h. The reaction was quenched with water and then extracted with EtOAc. The organics were washed with water, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 1% methanol/DCM. Yield 0.42g

MS: APCI (+ve): 266(M+1)

25

(ii) N-[5-(5-Chloro-2-hydroxyphenyl)pyrimidin-2-yl]-N-methylmethanesulfonamide
The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 2-hydroxy-5-chloroboronic acid (0.27g). Yield 0.2g

30 MS: APCI (+ve): 314(M+1)

(iii) (4-Chloro-2-{2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}phenoxy)acetic acid

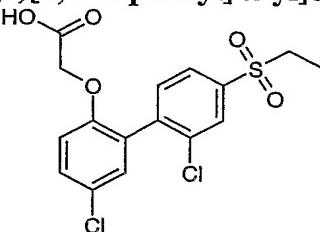
The title compound was prepared by the method of example 1 step (i) and (iii) using the product from step (ii). Yield 0.017g

¹H NMR DMSO-d₆: δ 13.16 (1H, s) ; 8.94 (2H, s) ; 7.57 (1H, d) ; 7.45-7.42 (1H, m) ; 7.14 (1H, d) ; 4.82 (2H, s) ; 3.55 (3H, s) ; 3.47 (3H, s)
MS: APCI (-ve): 370(M-1)

10

Example 26

[[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



(i) 2-Chloro-4-(ethylthio)-1-iodo- benzene

A solution of 3-chloro-4-iodo-aniline (5.6g), isoamylnitrite (8.8ml) and ethyldisulphide (13.4ml) in acetonitrile (100ml) was heated at 60°C for 24h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica eluting with 1% ethylacetate/isohexane. Yield 4.02g

¹H NMR CDCl₃: δ 7.70 (1H, d) ; 7.36 (1H, d) ; 6.87 (1H, dd) ; 2.94 (2H, q) ; 1.32 (3H, t)

(ii) [[[2',5-Dichloro-4'-(ethylthio)[1,1'-biphenyl]-2-yl]oxy]methyl]- benzene

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and the product from example 16 step (ii). Yield 3.64g

25

¹H NMR CDCl₃: δ 7.4 (1H, s) ; 7.32-7.18 (9H, m) ; 6.92 (1H, d) ; 5.03 (2H, s) ; 2.99 (2H, q) ; 1.36 (3H, t)

(iii) [[[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]methyl]- benzene

The subtitle compound was prepared by the method of example 2 step (i) using the product from step (ii). Yield 3.8g

¹H NMR CDCl₃: δ 8.00 (1H, s) ; 7.81 (1H, d) ; 7.48 (1H, d) ; 7.36-7.20 (7H, m) ; 6.95 (1H, d) ; 5.04 (2H, s) ; 3.16 (2H, q) ; 1.32 (3H, t)

(iv) 2',5-Dichloro-4'-(ethylsulfonyl)-[1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 16 step (iv) using the product from step (iii). Yield 2.44g

5

¹H NMR CDCl₃: δ 8.03 (1H, s) ; 7.85 (1H, d) ; 7.55 (1H, d) ; 7.30 (1H, d) ; 7.16 (1H, s) ; 6.92 (1H, d) ; 5.20 (2H, s) ; 3.17 (2H, q) ; 1.36 (3H, t)

(v) [[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid, ethyl ester
10 The subtitle compound was prepared by the method of example 1 step (i) using the product from step (iv) and ethylbromoacetate. Yield 2.23g

(vi) [[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
A mixture of the product from step (v) (2.23g), 1M aqueous sodium hydroxide (10ml) and
15 THF (20ml) was stirred at RT for 3h. The mixture was acidified with 2M hydrochloric acid, extracted with diethylether and the organics washed with water, dried, and evaporated under reduced pressure. The residue was recrystallised from ethylacetate/iso hexane, yield 0.45g.

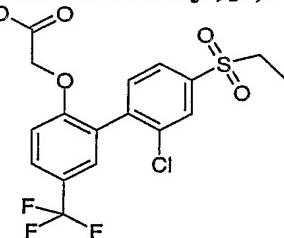
20 ¹H NMR CDCl₃: δ 13.02 (1H, s) ; 8.02 (1H, s) ; 7.89 (1H, d) ; 7.69 (1H, d) ; 7.48 (1H, dd) ; 7.34 (1H, d) ; 7.08 (1H, d) ; 4.70 (2H, s) ; 3.44 (2H, q) ; 1.16 (3H, t)

MS: APCI (-ve): 387/9 (M-1)

Mpt. 163-4°C

25 Example 27

[[2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



(i) 2-Bromo-1-(phenylmethoxy)-4-(trifluoromethyl)-benzene

The subtitle compound was prepared by the method of example 16 step (i) using 2-bromo-30 4-trifluoromethylphenol. Yield 58.7g

¹H NMR CDCl₃: δ 7.83 (1H, s) ; 7.51-7.32 (6H, m) ; 6.98 (1H, d) ; 5.21 (2H, s)

(ii) [2-(Phenylmethoxy)-5-(trifluoromethyl)phenyl]- boronic acid

The subtitle compound was prepared by the method of example 16 step (ii) using the product from step (i). Yield 30.7g

¹H NMR CDCl₃: δ 8.14 (1H, d) ; 7.68 (1H, dd) ; 7.44-7.39 (5H, m) ; 7.05 (1H, d) ; 5.79 (2H, s) ; 5.20 (2H, s)

(iii) [2-Hydroxy-5-(trifluoromethyl)phenyl]- boronic acid

The subtitle compound was prepared by the method of example 16 step (iv) using the product from step (ii). Yield 3.54g

(iv) 2'-Chloro-4'-(ethylthio)-5-(trifluoromethyl)- [1,1'-biphenyl]-2-ol

A mixture of palladium acetate (0.045g) and tri-p-tolylphosphine (0.213g) in methanol (10ml) was stirred at RT for 30min. The product from step (iii) (1g), sodium carbonate (1.27g), the product from example (26) step (i) (1.19g) and methanol (20ml) were added and the mixture heated under reflux for 6h. The solvent was removed under reduced pressure and the residue partitioned between diethylether and 2M hydrochloric acid. The organics were separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 10% ethylacetate/isohexane. Yield 0.503g

MS: ESI (-ve): 331/3 (M-1)

(v) 2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)- [1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 2 step (i) using the product from step (iv). Yield 0.277g

MS: ESI (-ve): 363/5 (M-1)

(vi) [[2'-chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 1 step (i) using the product from step (v). Yield 0.253g

(vii) [[2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

The title compound was prepared by the method of example 1 step (iii) using the product from step (vi). Yield 0.154g

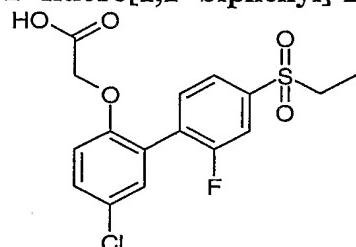
¹H NMR CDCl₃: δ 13.12 (1H, s) ; 8.04 (1H, s) ; 7.91 (1H, d) ; 7.81 (1H, d) ; 7.72 (1H, d) ; 7.63 (1H, s) ; 7.25 (1H, d) ; 4.82 (2H, s) ; 3.45 (2H, q) ; 1.17 (3H, t)

MS: APCI (-ve): 421/3 (M-1)

5 Mpt. 167°C

Example 28

[[5-Chloro-4'-(ethylsulfonyl)-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]- acetic acid



10 (i) 1-Bromo-4-(ethylthio)-2-fluoro-benzene

Bromine (0.3ml) was added to a solution of 1-ethylsulfanyl-3-fluoro-benzene (1g) in chloroform (20ml) at 0°C then warmed to RT. After 2h the mixture was diluted with DCM, washed with aq. sodium thiosulphate solution, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 10% diethylether/iso-hexane. Yield 1.2g

15

¹H NMR CDCl₃: δ 7.44–6.93 (3H, m) ; 2.99–2.90 (2H, q) ; 1.42–1.30 (3H, t).

(ii) 1-Bromo-4-(ethylsulfonyl)-2-fluoro-benzene

20 The subtitle compound was prepared by the method of example 2 step (i) using the product from step (i). Yield 0.94g

¹H NMR CDCl₃: δ 7.81–7.07 (3H, m) ; 3.17–3.10 (2H, q) ; 1.32–1.19 (3H, t).

25 (iii) [[[5-Chloro-4'-(ethylsulfonyl)-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]methyl]-benzene

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (ii) and the product from example 16 step (ii). Yield 0.55g

30

(iv) 5-Chloro-4'-(ethylsulfonyl)-2'-fluoro-[1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 16 step (iv) using the product from step (ii), yield 0.35g

MS: ESI (-ve) 313 (M-1)

(v) [[5-Chloro-4'-(ethylsulfonyl)-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]- acetic acid

The title compound was prepared by the method of example 1 step (i) and step (iii) using
5 the product from step (iv), yield 0.205g

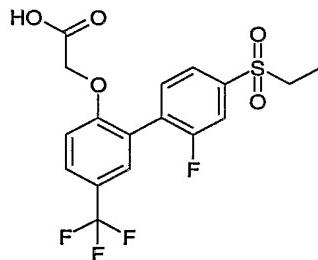
¹H NMR DMSO-d₆: δ 7.81–7.08 (6H, m) ; 4.73 (2H, s) ; 3.44-3.39 (2H, q) ; 1.17-1.14 (3H, t).

MS: ESI (-ve) 371 (M-1)

10

Example 29

[[4'-(Ethylsulfonyl)-2'-fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-acetic acid,
sodium salt



15

The title compound was prepared by the method of example 28, yield 0.26g.

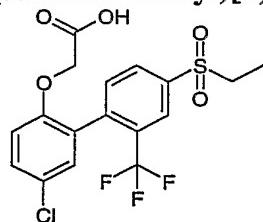
¹H NMR DMSO-d₆: δ 7.96–7.57(5H, m) ; 7.09-7.07 (1H, d) ; 4.31 (2H, s) ; 3.44-3.35 (2H, q) ; 1.18-1.14 (3H, t).

MS: ESI (-ve) 405 (M-1)

20

Example 30

[[5-Chloro-4'-(ethylsulfonyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



(i) 1-Bromo-4-(ethylthio)-2-(trifluoromethyl)- benzene

25 Iodoethane (0.84ml) was added to a stirred solution of 3-trifluoromethyl-thiophenol (2g) and potassium carbonate (1.42g) in DMF (20ml). After 72h the mixture was partitioned between diethylether and water, the organics separated, dried and evaporated under reduced pressure. The residue was dissolved in acetic acid (20ml), cooled to 0°C, then bromine (0.51ml) added. The mixture was stirred at RT for 16h, the solvent removed

under reduced pressure and the residue purified by chromatography on silica eluting with 25% DCM/iso-hexane. Yield 2.05g

(ii) 5-Chloro-4'-(ethylthio)-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol

5 The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 5-chloro-2-hydroxyphenyl-boronic acid, yield 0.26g

MS: ESI (-ve) 347 (M-1)

10 (iii) [[5-Chloro-4'-(ethylthio)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 1 step (i) using the product from step (ii), yield 0.26g

15 MS: APCI (-ve) 389/391 (M-1) – t-butyl

(iv) [[5-Chloro-4'-(ethylsulfonyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-acetic acid

20 The title compound was prepared by the method of example 2 step (i) and example 1 step (iii) using the product from step (iii), yield 0.045g

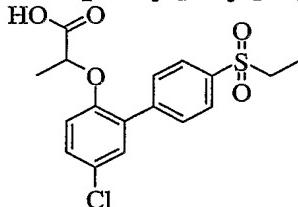
¹H NMR DMSO-d6: δ 7.62–7.01 (6H, m) ; 4.69–4.66 (2H, s) ; 4.20–4.10 (2H, q) ; 1.40–1.35 (3H, t).

MS: ESI (-ve) 421 (M-1)

25

Example 31

2-[[5-Chloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-propanoic acid



(i) 2-(2-Bromo-4-chlorophenoxy)-propanoic acid, 1,1-dimethylethyl ester

30 The subtitle compound was prepared by the method of example 1 step (i) using 2-bromo-4-chlorophenol and 2-bromopropionic acid, tert-butyl ester, yield 1.1g

¹H NMR DMSO-d6: δ 7.54–7.16 (2H, m) ; 6.74–6.71 (1H, d) ; 3.70 (3H, s) ; 1.78–1.76 (1H, d) ; 1.48 (9H, s).

(ii) 2-[[5-Chloro-4'-(ethylthio)[1,1'-biphenyl]-2-yl]oxy]- propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 4-(ethylthio)benzeneboronic acid, yield 1.2g.

MS: APCI (-ve) 336 (M-1) – t-butyl

(iii) 2-[[5-Chloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-propanoic acid

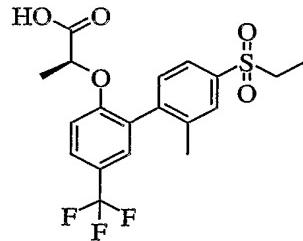
The title compound was prepared by the method of example 2 step (i) and example 1 step (iii) using the product from step (ii), yield 0.08g

¹H NMR DMSO-d₆: δ 7.97–6.96 (7H, m) ; 4.79–4.76 (1H, m) ; 3.39–3.31 (2H, t) ; 1.39–1.37 (3H, d) ; 1.16–1.07 (3H, t).

MS: ESI (-ve) 367 (M-1)

Example 32

2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



20

(i) 1-Bromo-4-(ethylsulfonyl)-2-methyl-benzene

The subtitle compound was prepared by the method of example 2 step (i) using the product from example 10 step (i), yield 4.3g.

25 MS: ESI (+ve) 264 (M+1)

(ii) [2-(Phenylmethoxy)-5-(trifluoromethyl)phenyl]-boronic acid

The subtitle compound was prepared by the method of example 16 step (ii) using the product from example 27 step (i), yield 5.5g.

30

¹H NMR CDCl₃: δ 8.14–7.62 (2H, m) ; 7.43–7.38 (5H, m) ; 7.01 (1H, m) ; 5.67 (2H, s) ; 5.19–5.16 (2H, s)

(iii) [[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]methyl]-benzene

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and (ii), yield 2.72g.

5

MS: ESI (+ve) 452 (M+1+NH₃)

(iv) 4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 16 step (iv) using the product from step (iii), yield 2.1g.

10

MS: ESI (+ve) 362 (M+1+NH₃)

(v) 2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid, methyl ester

15

Diethyl azodicarboxylate (0.14ml) was added to a stirred solution of the product from step (iv) (0.3g), methyl-R-lactate (0.083ml) and triphenylphosphine (0.228g) in THF (10ml) at 0°C. After 4h, the mixture was diluted with water and extracted with ethylacetate, the organics separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 50% diethylether/iso-hexane. Yield 0.4g

20

MS: ESI (+ve) 448 (M+1+NH₃)

(vi) 2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

25

A mixture of the product from step (v) (0.4g) and lithium hydroxide (2 equiv) in THF (10ml) and water (10ml) was stirred at RT overnight. The mixture was partitioned between ethylacetate/water, the aqueous layer was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic layer was dried, evaporated under reduced pressure and the residue purified by reverse phase HPLC. Yield 0.035g

30

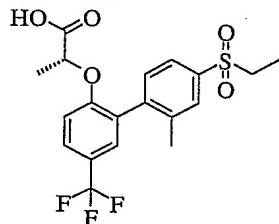
¹H NMR DMSO-d6: δ 7.78–7.44 (5H, m) ; 7.16-7.14 (1H, d) ; 4.91-4.86 (1H, q) ; 3.30-3.25 (2H, q) ; 2.22 (3H, s) ; 1.33-1.24 (3H, d) ; 1.10-1.07 (3H, t).

MS: ESI (+ve) 434 (M+1+NH₃)

35

Example 33

2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2R)-propanoic acid, sodium salt

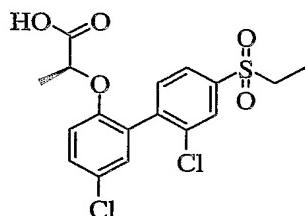


The title compound was prepared by the method of example 32 using methyl-S-lactate, yield 0.2g.

- 5 ^1H NMR DMSO-d₆: δ 7.77–7.38 (5H, m) ; 7.02-7.00 (1H, d) ; 4.32 (1H, m) ; 3.39-3.25 (2H, q) ; 2.32 (3H, s) ; 1.21-1.07 (6H, d+t).
 MS: ESI (+ve) 434 (M+1+NH₃)

Example 34

- 10 **2-[[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)- propanoic acid, sodium salt**

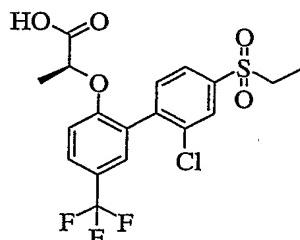


The title compound was prepared by the method of example 32 step (v) and (vi) using the product from example 26 step (iv), yield 0.18g.

- 15 ^1H NMR DMSO-d₆: δ 7.99–7.23 (5H, m) ; 6.93-6.91(1H, d) ; 4.26-4.24 (1H, q) ; 3.46-3.37 (2H, q) ; 1.20-1.06 (6H, d+t).
 MS: ESI (-ve) 402/403 (M-1)

20 **Example 35**

- 2-[[2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)- propanoic acid**



- 25 The title compound was prepared by the method of example 32 step (v) and (vi) using the product from example 2 step (v), yield 0.05g.

¹H NMR DMSO-d₆: δ 7.98–7.23 (5H, m) ; 6.93–6.91 (1H, d) ; 4.68 (1H, m) ; 3.20–3.15

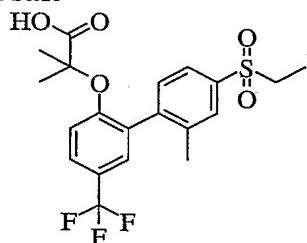
(2H, q) ; 1.48–1.39 (3H, m) ; 1.34–1.30 (3H, t)..

MS: ESI (-ve) 436 (M-1)

5

Example 36

2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-2-methyl-propanoic acid, sodium salt



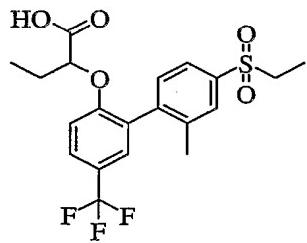
10 The title compound was prepared by the method of example 1 step (i) and example 26 step (vi) using the product from example 34 step (iv), yield 0.18g.

¹H NMR DMSO-d₆: δ 7.72 (1H, s) ; 7.71 (1H, d) ; 7.56 (1H, d) ; 7.44 (1H, d) ; 7.35 (1H, s) ; 7.10 (1H, d) ; 2.29 (3H, s) ; 1.38 (6H, s) ; 1.13 (3H, t)

15 MS: ESI (-ve) 429 (M-1)

Example 37

2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-butanoic acid, sodium salt



20

The title compound was prepared by the method of example 1 step (i) and example 26 step (vi) using the product from example 34 step (iv), yield 0.29g.

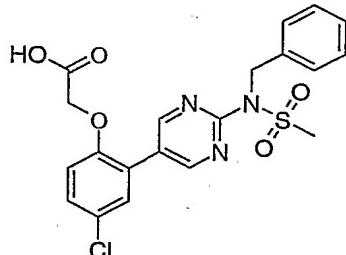
¹H NMR DMSO-d₆: δ 7.78 (1H, s) ; 7.71 (1H, d) ; 7.64 (1H, d) ; 7.41 (1H, s) ; 7.01 (1H,

25 d) ; 4.27 (1H, brs) ; 3.36 (2H, q) ; 2.33 (3H, brs) ; 1.64–1.55 (2H, m) ; 1.11 (3H, t) ; 0.66 (3H, brs)

MS: ESI (-ve) 429 (M-1)

Example 38

[4-Chloro-2-[2-[(methylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic acid



- (i) *N*-(5-Bromo-2-pyrimidinyl)-*N*-(phenylmethyl)-methanesulfonamide
 5 Sodium hydride (0.1g, 60% disp. in oil) was added to a stirred solution of benzyl-(5-bromo-pyrimidin-2-yl)-amine (0.55g) in DMF (8ml) at 0°C. After 30min methanesulphonyl chloride (0.286g) was added and the mixture stirred at RT for 2h then partitioned between ethyl acetate and water. The organics were separated washed with water, dried and evaporated under reduced pressure. The residue was purified by
 10 chromatography on silica eluting with dichloromethane. Yield 0.41g

MS: APCI (+ve) 344 (M+1)

- (ii) *N*-[5-(5-Chloro-2-hydroxyphenyl)-2-pyrimidinyl]-*N*-(phenylmethyl)-methanesulfonamide
 15 The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 5-chloro-2-hydroxyphenyl-boronic acid , yield 0.25g.

MS: APCI (+ve) 390 (M+1)

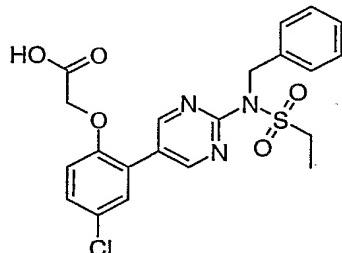
- (iii) [4-Chloro-2-[2-[(methylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic acid
 20 The title compound was prepared by the method of example 1 step (i) and step (iii) using the product from step (ii), yield 0.07g.

¹H NMR DMSO-d6: δ 13.16 (1H, s) ; 8.93 (2H, s) ; 7.56 (1H, d) ; 7.44-7.41 (1H, m) ; 7.37-7.31 (4H, m) ; 7.27-7.23 (1H, m) ; 7.12 (1H, d) ; 5.28 (2H, s) ; 4.81 (2H, s) ; 3.59 (3H, s).

- 30 MS: APCI (-ve): 446 (M-1)

Example 39

[4-Chloro-2-[2-[(ethylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic acid



(i) *N*-(5-Bromo-2-pyrimidinyl)-*N*-(phenylmethyl)-ethanesulfonamide

5 The subtitle compound was prepared by the method of example 38 step (i) using benzyl-(5-bromo-pyrimidin-2-yl)-amine and ethanesulphonyl chloride , yield 0.31g.

MS: APCI (+ve) 358 (M+1)

10 (ii) *N*-[5-(5-Chloro-2-hydroxyphenyl)-2-pyrimidinyl]-*N*-(phenylmethyl)-ethanesulfonamide

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 5-chloro-2-hydroxyphenyl-boronic acid , yield 0.25g.

15 MS: APCI (+ve) 404 (M+1)

(iii) [4-Chloro-2-[2-[(ethylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic acid

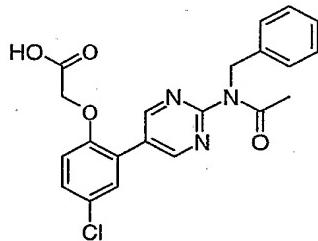
20 The title compound was prepared by the method of example 1 step (i) and step (iii) using the product from step (ii), yield 0.13g.

¹H NMR DMSO-d6: δ 13.14 (1H, s) ; 8.92 (2H, s) ; 7.56 (1H, d) ; 7.44-7.31 (5H, m) ; 7.27-7.23 (1H, m) ; 7.12 (1H, d) ; 5.27 (2H, s) ; 4.81 (2H, s) ; 3.87 (2H, q) ; 1.25 (3H, t).

25 MS: APCI (-ve): 460 (M-1)

Example 40

[2-[2-[Acetyl(phenylmethyl)amino]-5-pyrimidinyl]-4-chlorophenoxy]-acetic acid

(i) *N*-(5-Bromo-2-pyrimidinyl)-*N*-(phenylmethyl)-acetamide

The subtitle compound was prepared by the method of example 38 step (i) using benzyl-(5-bromo-pyrimidin-2-yl)-amine and acetylchloride , yield 0.21g.

5

MS: APCI (+ve) 306 (M+1)

(ii) *N*-[5-(5-Chloro-2-hydroxyphenyl)-2-pyrimidinyl]-*N*-(phenylmethyl)-acetamide

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 5-chloro-2-hydroxyphenyl-boronic acid , yield 0.16g.

10

MS: APCI (+ve) 354 (M+1)

(iii) [2-[2-[Acetyl(phenylmethyl)amino]-5-pyrimidinyl]-4-chlorophenoxy]-acetic acid

15 The title compound was prepared by the method of example 1 step (i) and step (iii) using the product from step (ii), yield 0.08g.

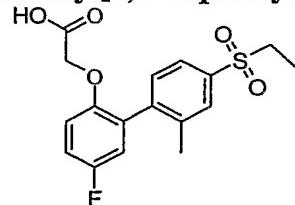
¹H NMR DMSO-d6: δ 9.01 (2H, s) ; 7.59 (1H, d) ; 7.44 (1H, q) ; 7.30-7.18 (5H, m) ; 7.13 (1H, d) ; 5.26 (2H, s) ; 4.81 (2H, s) ; 2.45 (3H, s).

20

MS: APCI (+ve): 412 (M+1)

Example 41

[[4'-(Ethylsulfonyl)-5-fluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid



(i) [4-(Ethylthio)-2-methylphenyl]-boronic acid

A 100ml portion of a solution of the product from example 10 step (i) (120.7g) in THF (500ml) was added to a stirred mixture of magnesium turnings (13.4g) in THF (100ml). Dibromoethane (0.2ml) was added, and the mixture gently refluxed on initiation. The remaining bromide solution was added dropwise maintaining the reaction at reflux. After addition the mixture was allowed to cool to RT then transferred via cannula into a stirred

25

30

solution of trimethylborate (112ml) in THF (200ml) at 0°C. The mixture was warmed to RT, stirred for 2h then quenched with 2M hydrochloric acid (300ml). After stirring at RT for 18h the THF was removed under reduced pressure and the mixture extracted with diethylether. The organics were separated, washed with water, dried and evaporated under reduced pressure. The residue was triturated with diethylether/iso hexane and filtered. Yield 53.02g

¹H NMR CDCl₃: δ 8.08 (1H, d) ; 7.18 (1H, d) ; 7.15 (1H, s) ; 3.04 (2H, q) ; 2.76 (3H, s) ; 1.38 (3H, t)

10

(ii) (2-Bromo-4-fluorophenoxy)-acetic acid, 1,1-dimethylethyl ester
The subtitle compound was prepared by the method of example 1 step (i).

(iii) [[4'-(Ethylsulfonyl)-5-fluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid

15

The title compound was prepared by the method of example 27 step (iv), example 2 step (i) and example 1 step (iii) using the products from step (i) and (ii), yield 0.045g.

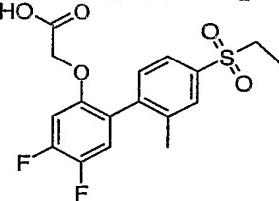
¹H NMR DMSO-d6: δ 7.8-7.64 (2H, m) ; 7.42 (2H, d) ; 7.8-6.0 (3H, m) ; 4.10 (2H, s) ; 3.20 (2H, q) ; 1.18 (3H, t)

20

MS: APCI (-ve): 351 (M-1)

Example 42

[[4'-(Ethylsulfonyl)-4,5-difluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid



25 The title compound was prepared by the method of example 41, yield 0.081g.

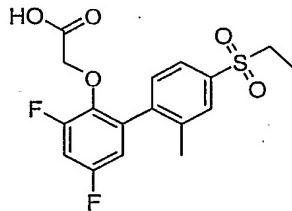
¹H NMR DMSO-d6: δ 7.76 (1H, s) ; 7.71 (1H, dd) ; 7.44 (1H, d) ; 7.23 (1H, t) ; 7.01-6.94 (1H, m) ; 4.32 (2H, s) ; 3.39 (2H, m) ; 2.25 (3H, s) ; 1.18 (3H, t)

MS: APCI (-ve): 369 (M-1)

30

Example 43

[[4'-(Ethylsulfonyl)-3,5-difluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid



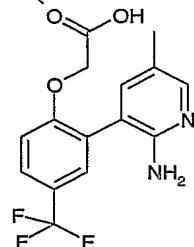
The title compound was prepared by the method of example 41, yield 0.15g.

¹H NMR DMSO-d₆: δ 7.82-7.70 (2H, m); 7.49-7.38 (2H, m); 7.02-6.90 (1H, m); 4.40

5 (2H, d); 3.34 (2H, q); 1.11 (3H, t)

Example 44

[2-(2-Amino-5-methyl-3-pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid



10 (i) [4-(Trifluoromethyl)phenoxy]- acetic acid

Sodium hydride (2.96g, 60% disp. in oil) was added to a stirred solution of 4-hydroxybenzo-trifluoride (10g) in tetrahydrofuran (150ml) at -78°C. The cooling bath was removed, the mixture stirred for 1h then methyl bromoacetate (7ml) added. After 1h, water was added, the tetrahydrofuran evaporated off under reduced pressure and the residue partitioned between ethyl acetate/2M hydrochloric acid. The organic layer was evaporated under reduced pressure and the residue dissolved in tetrahydrofuran (120ml). Methanol (30ml), water (30ml) and conc. sodium hydroxide solution (6ml) was added and the mixture stirred at RT overnight. The organics were removed under reduced pressure and the residue partitioned between ethylacetate and 2M hydrochloric acid. The organics were separated, dried and evaporated under reduced pressure, yield 12.42g

15 ¹H NMR DMSO-d₆: δ 13.13 (1H, s); 7.65 (2H, d); 7.10 (2H, d); 4.80 (2H, s).

20 MS: APCI (-ve) 219 (M-1)

(ii) [4-(Trifluoromethyl)phenoxy]- acetic acid, (3-methyl-3-oxetanyl)methyl ester

25 Oxalyl chloride (14ml) was added to a solution of the product from step (i) (12.42g) and N,N-dimethylformamide (2 drops) in dichloromethane (100ml), and stirred at RT for 72h. The mixture was evaporated under reduced pressure, the residue dissolved in dichloromethane (100ml) then triethylamine (20ml) and 3-methyl-3-oxetanemethanol (17ml) added. After 2h the mixture was washed with water, evaporated under reduced

pressure and the residue purified by chromatography on silica eluting with dichloromethane, yield 14.2g.

¹H NMR DMSO-d6: δ 7.66 (2H, d); 7.14 (2H, d); 4.98 (2H, s), 4.34 (2H, d); 4.24 (2H, s); 4.19 (2H, d), 1.21 (3H, s).

(iii) 4-Methyl-1-[[4-(trifluoromethyl)phenoxy]methyl]- 2,6,7-trioxabicyclo[2.2.2]octane

Boron trifluoride diethyl etherate (1.48ml) was added to a solution of the product from step (ii) (14.2g) in dichloromethane at -78°C. The cooling bath was removed, the mixture stirred for 3h then triethylamine (6.2ml) added. The mixture was reduced to half the volume under reduced pressure then filtered. The filtrate was evaporated under reduced pressure then the residue purified by chromatography on silica (pre-eluted with one column volume of neat triethylamine) eluting with dichloromethane, yield 11.1g.

¹H NMR DMSO-d6: δ 7.62 (2H, d); 7.14 (2H, d); 4.04 (2H, s); 3.91 (6H, s); 0.77 (3H, s).
MS: APCI (+ve) 305 (M+1)

(iv) [2-Borono-4-(trifluoromethyl)phenoxy]- acetic acid

A solution of sec-butyllithium (66ml, 1.4M in cyclohexane) was added dropwise over 10min to a stirred solution of the product from step (iii) (9.44g) in THF (100ml) at -78°C. After 3h the mixture was warmed to -40°C for 5min, then cooled to -78°C. Trimethylborate (14.1ml) was added, then after 10min the reaction quenched with 2M hydrochloric acid. The mixture was warmed to RT and the organic phase separated. The aqueous layer was extracted with ethylacetate, the organics combined and evaporated under reduced pressure. The residue was dissolved in methanol (500ml) then bondelut-NH₂ resin(180g) added and the mixture swirled for 0.5h then filtered. The resin was washed with 10% acetic acid /methanol, the washings then evaporated under reduced pressure and dried under high vacuum. The residue was dissolved in methanol(50ml), tetrahydrofuran (50ml) and saturated aqueous sodium hydroxide solution (2ml), left for 30min then 2M hydrochloric acid (50ml) added and the organics evaporated under reduced pressure. The residual aqueous layer was extracted with ethylacetate, the organics separated, dried and evaporated under reduced pressure, yield 5.05g.

¹H NMR DMSO-d6: δ 8.07 (1H, s); 7.89 (1H, d); 7.75 (1H, dd); 7.14 (1H, d); 4.85 (2H, s).

MS: APCI (-ve) 263 (M-1)

(v) [2-(2-Amino-5-methyl-3-pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid

A mixture of the product from step (iv) (0.1g), 2-amino-3-bromo-5-methylpyridine (0.071g), tetrakis(triphenylphosphine)palladium(0) (0.046g), sodium carbonate (0.12g) in methanol (2ml) was heated in a CEM microwave (variable wattage up to 150W) at 100°C for 10min. The mixture was loaded onto SCX resin (sulphonic acid resin), flushed with methanol then the product eluted with methanol/ammonia. The methanol/ammonia filtrate was evaporated under reduced pressure then loaded onto bondelut-NH₂ resin. The resin was flushed with methanol then the product eluted with methanol/acetic acid. The methanol/acetic acid filtrate was evaporated and the residue purified by RPHPLC. Yield 0.089g

10

¹H NMR DMSO-d6: δ 7.87 (1H, s); 7.79 (1H, d); 7.69 (1H, s); 7.63 (1H, s); 7.26 (1H, d); 4.9 (2H, s); 2.2 (3H, s).

MS: APCI (-ve) 325 (M-1)

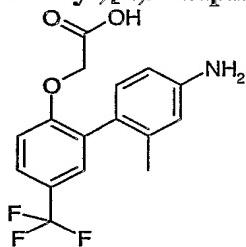
15

Example 45-123

The following compounds were synthesised in an analogous method to example 44

Example 45

[[4'-Amino-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



20

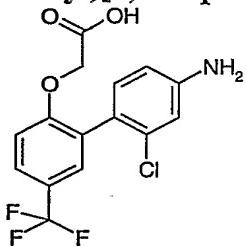
¹H NMR DMSO-d6: δ 7.62 (1H, d); 7.32 (1H, s); 7.05 (1H, d); 6.81 (1H, d); 6.47 (1H, s); 6.44 (1H, d); 4.74 (2H, s); 1.98 (3H, s).

MS: APCI (-ve) 324 (M-1)

25

Example 46

[[4'-Amino-2'-chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

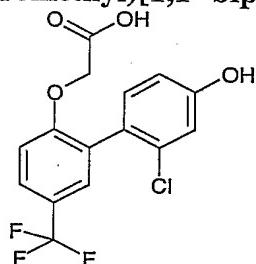


¹H NMR DMSO-d6: δ 7.65 (1H, d); 7.4 (1H, s), 7.15 (1H, d); 7.04 (1H, d); 6.7 (1H, s); 6.56 (1H, d); 4.76 (2H, s).

MS: APCI (-ve) 344/6 (M-1)

Example 47

[[2'-Chloro-4'-hydroxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



5

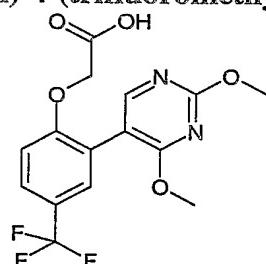
¹H NMR DMSO-d₆: δ 9.98 (1H, s); 7.69 (1H, d); 7.44 (1H, s); 7.21 (1H, d); 7.14 (1H, d); 6.91 (1h, s); 6.80 (1H, d); 4.76 (2H, s).

MS: APCI (-ve) 345/7 (M-1)

10

Example 48

[2-(2,4-Dimethoxy-5-pyrimidinyl)-4-(trifluoromethyl)phenoxy]- acetic acid



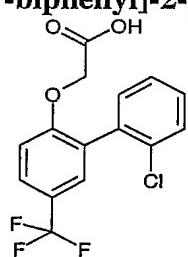
¹H NMR DMSO-d₆: δ 8.32 (1H, s); 7.71 (1H, d); 7.63 (1H, s); 7.20 (1H, d); 4.8 (2H, s); 3.95 (3H, s); 3.87 (3H, s).

15

MS: APCI (-ve) 357 (M-1)

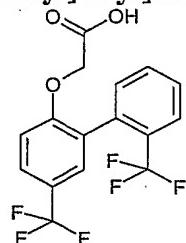
Example 49

[[2'-Chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



20 ¹H NMR DMSO-d₆: δ 7.75 (1H, d); 7.55 (1H, m), 7.50 (1H, s); 7.42 (1H, m); 7.41(1H, d); 7.40 (1H, d); 7.19 (1H, d); 4.78 (2H, s).

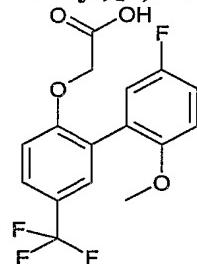
MS: APCI (-ve) 329/31 (M-1)

Example 50**[[2',5-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.83 (1H, d); 7.75 (1H, d); 7.71 (1H, d); 7.63 (1H, t); 7.44 (1H, s);

5 7.43 (1H, d); 4.74 (2H, m).

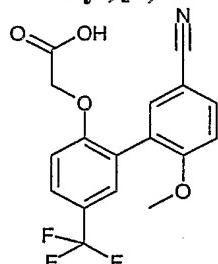
MS: APCI (-ve) 363 (M-1)

Example 51**[[5'-Fluoro-2'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.68 (1H, d); 7.51 (1H, s); 7.20 (1H, d); 7.17 (1H, m); 7.15 (1H, m);

10 7.10 (1H, d); 4.78 (2H, s); 3.7 (3H, s).

MS: APCI (-ve) 343 (M-1)

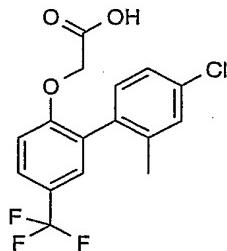
Example 52**[[5'-Cyano-2'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.87 (1H, d); 7.74 (1H, s); 7.71 (1H, d); 7.56 (1H, s); 7.29 (1H, d);

15 7.19 (1H, d); 4.77 (2H, s); 3.81 (3H, s).

MS: APCI (-ve) 350 (M-1)

Example 53**[[4'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**



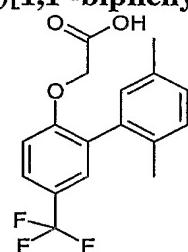
¹H NMR DMSO-d₆: δ 7.71 (1H, d), 7.47 (1H, s), 7.34 (1H, d), 7.30 (1H, d), 7.24 (1H, s), 7.13 (1H, d), 4.73 (2H, s), 2.11 (3H, s)

MS: APCI (-ve) 343 / 345 (M-1)

5

Example 54

[[2',5'-Dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

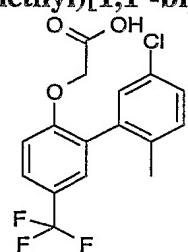


¹H NMR DMSO-d₆: δ 7.64 (1H, d), 7.35 (1H, s), 7.13 (1H, d), 7.07 (1H, d), 7.02 (1H, d), 6.94 (1H, s), 4.50 (2H, s), 2.30 (3H, s), 2.08 (3H, s)

MS: APCI (-ve) 323 (M-1)

Example 55

[[5'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



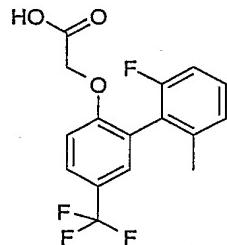
¹H NMR DMSO-d₆: δ 7.70 (1H, d), 7.43 (1H, s), 7.38 (1H, s), 7.29 (1H, d), 7.19 (1H, d), 7.14 (1H, s), 4.70 (2H, s), 2.14 (3H, s)

MS: APCI (-ve) 343/345 (M-1)

15

Example 56

[[2'-Fluoro-6'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



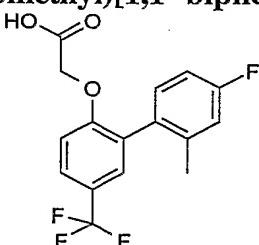
¹H NMR DMSO-d₆: δ 7.71 (1H, d), 7.44 (1H, s), 7.27 (1H, q), 7.18 (1H, t), 7.11 (1H, d), 7.04 (1H, d), 4.67 (2H, s), 2.06 (3H, s)

MS: APCI (-ve) 327 (M-1)

5

Example 57

[[4'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



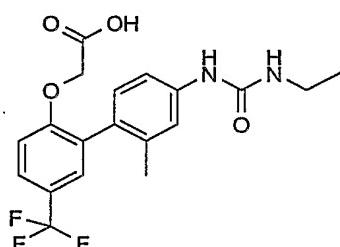
¹H NMR DMSO-d₆: δ 7.70 (1H, d), 7.42 (1H, s), 7.30 (1H, t), 7.12 (1H, d), 7.10 (1H, d),

10 7.04 (1H, d), 4.69 (2H, s), 2.11 (3H, s)

MS: APCI (-ve) 327 (M-1)

Example 58

[[4'-[[Ethylamino]carbonyl]amino]-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



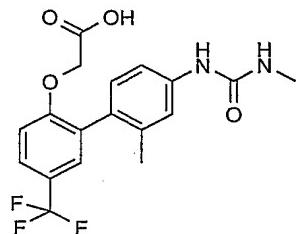
¹H NMR DMSO-d₆: δ 8.49 (1H, s), 7.62 (1H, d), 7.31 (1H, s), 7.29 (1H, s), 7.24 (1H, d), 7.04 (1H, d), 7.00 (1H, d), 6.25 (1H, t), 4.60 (2H, s), 3.10 (2H, m), 1.06 (3H, t)

MS: APCI (-ve) 395 (M-1)

20

Example 59

[[2'-Methyl-4'-[[methylamino]carbonyl]amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

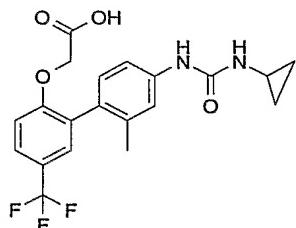


¹H NMR DMSO-d₆: δ 8.52 (1H, s), 7.65 (1H, d), 7.39 (1H, s), 7.26 (1H, s), 7.26 (1H, d), 7.07 (1H, d), 7.00 (1H, d), 6.05 (1H, d), 4.72 (2H, s), 2.09 (3H, s)
MS: APCI (+ve) 383 (M+1)

5

Example 60

[[4'-(Cyclopropylamino)carbonyl]amino]-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

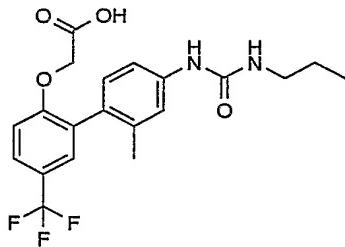


¹H NMR DMSO-d₆: δ 8.33 (1H, s), 7.66 (1H, d), 7.37 (1H, s), 7.31 (1H, s), 7.26 (1H, d), 7.08 (1H, d), 7.00 (1H, d), 6.46 (1H, s), 4.75 (2H, s), 2.54 (1H, m), 0.63 (2H, m), 0.42 (2H, m)
MS: APCI (+ve) 409 (M+1)

15

Example 61

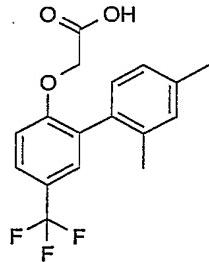
[[2'-Methyl-4'-(Propylamino)carbonyl]amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid,



¹H NMR DMSO-d₆: δ 8.48 (1H, s), 7.64 (1H, d), 7.36 (1H, s), 7.30 (1H, s), 7.24 (1H, d), 7.07 (1H, d), 7.00 (1H, d), 6.23 (1H, t), 4.68 (2H, s), 3.05 (2H, q), 2.10 (3H, s), 1.44 (2H, m), 0.88 (3H, d)
MS: APCI (+ve) 411 (M+1)

Example 62

[[2',4'-Dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



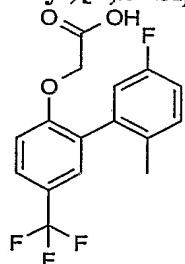
¹H NMR DMSO-d₆: δ 7.63 (1H, d), 7.34 (1H, s), 7.03 (4H, m), 4.50 (2H, s), 2.32 (3H, s), 2.11 (3H, s)

MS: APCI (-ve) 323 (M-1)

5

Example 63

[[5'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d₆: δ 7.65 (1H, d), 7.38 (1H, s), 7.29 (1H, d), 7.27 (1H, d), 7.11 (1H, d),

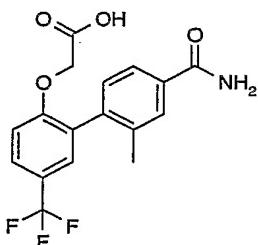
10 7.06 (1H, m), 4.40 (2H, s), 2.13 (3H, s)

MS: APCI (-ve) 327 (M-1)

Example 64

[[4'-(Aminocarbonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

15



¹H NMR DMSO-d₆: δ (1H, s), 7.77 (1H, s), 7.70 (1H, d), 7.63 (1H, d), 7.34 (1H, s), 7.30

(1H, s), 7.25 (1H, d), 6.98 (1H, d), 4.22 (2H, s), 2.21 (3H, s)

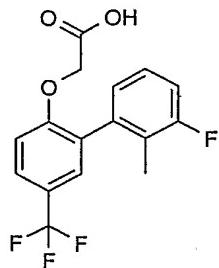
MS: APCI (+ve) 354 (M+1)

20

Example 65

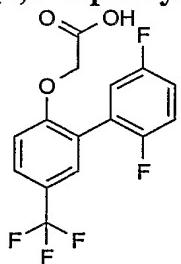
[[3'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

64



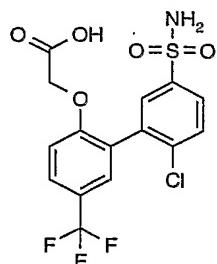
¹H NMR DMSO-d₆: δ 7.66 (1H, d), 7.40 (1H, s), 7.27 (1H, d), 7.24 (1H, d), 7.16 (1H, t), 7.05 (1H, d), 4.45 (2H, s), 2.07 (3H, s)
 MS: APCI (1ve) 327 (M-1)

5

Example 66**[[2',5'-Difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.68 (1H, d), 7.58 (1H, s), 7.53 (1H, m), 7.30 (1H, m), 7.28 (1H, m), 7.09 (1H, d), 4.44 (2H, s)

10

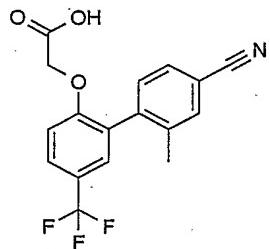
Example 67**[[5'-(Aminosulfonyl)-2'-chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

15

¹H NMR DMSO-d₆: δ 7.93 (1H, d), 7.82 (1H, d), 7.76 (1H, s), 7.73 (1H, d), 7.53 (1H, s), 7.10 (1H, d), 4.38 (2H, s)
 MS: APCI (+ve) 408/410 (M+1)

20

Example 68**[[4'-Cyano-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**



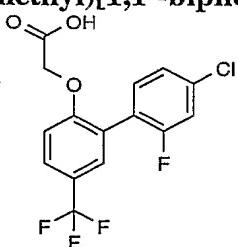
¹H NMR DMSO-d₆: δ 7.78 (1H, s), 7.71 (1H, t), 7.71 (1H, m), 7.46 (1H, s), 7.40 (1H, d), 7.11 (1H, d), 4.61 (2H, s), 2.18 (3H, s)

MS: APCI (-ve) 334 (M-1)

5

Example 69

[[4'-Chloro-2'-fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

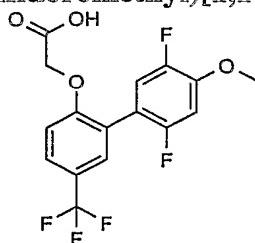


¹H NMR DMSO-d₆: δ 7.73 (1H, d), 7.60 (1H, s), 7.56 (1H, s), 7.52 (1H, d), 7.36 (1H, d), 7.17 (1H, d), 4.70 (2H, s)

10

Example 70

[[2',5'-Difluoro-4'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

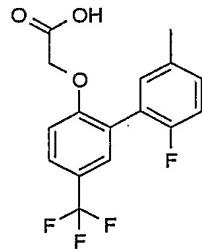


15

¹H NMR DMSO-d₆: δ 7.63 (1H, d), 7.60 (1H, m), 7.52 (1H, s), 7.19 (1H, m), 7.06 (1H, d), 4.39 (2H, s), 3.91 (3H, s)

Example 71

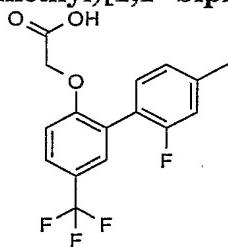
[[2'-fluoro-5'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d6: δ 7.74 (1H, d), 7.57 (1H, s), 7.25 (1H, d), 7.26 (1H, s), 7.19 (1H, d), 7.14 (1H, d), 4.85 (2H, s), 2.35 (3H, s)

5 **Example 72**

[[2'-Fluoro-4'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

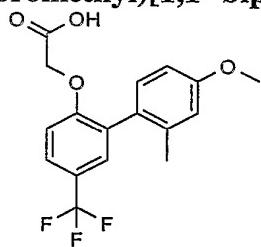


¹H NMR DMSO-d6: δ 7.67 (1H, d), 7.46 (1H, s), 7.40 (1H, t), 7.10 (1H, d), 7.07 (1H, d), 7.07 (1H, s), 4.49 (2H, s), 2.34 (3H, s)

10

Example 73

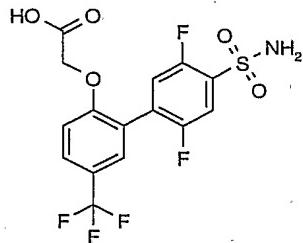
[[4'-Methoxy-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d6: δ 7.62 (1H, d), 7.33 (1H, s), 7.08 (1H, d), 7.00 (1H, d), 6.82 (1H, s), 6.78 (1H, d), 4.45 (2H, s), 3.80 (3H, s), 2.13 (3H, s)

Example 74

[[4'-(Aminosulfonyl)-2',5'-difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



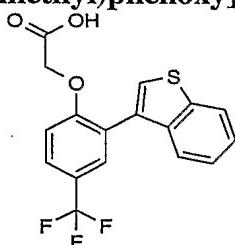
¹H NMR DMSO-d₆: δ 7.83 (1H, m), 7.75 (1H, d), 7.69 (1H, s), 7.63 (1H, m), 7.18 (1H, d), 4.53 (2H, s)

MS: APCI (-ve) 410 (M-1)

5

Example 75

[2-Benzo[b]thien-3-yl-4-(trifluoromethyl)phenoxy]- acetic acid



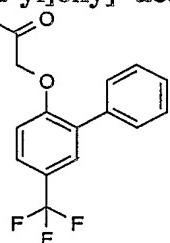
¹H NMR DMSO-d₆: δ 8.04 (1H, d), 7.87 (1H, s), 7.78 (1H, d), 7.69 (1H, d), 7.67 (1H, s),

10 7.38 (2H, m), 7.24 (1H, d), 4.81 (2H, s)

MS: APCI (-ve) 351 (M-1)

Example 76

[[5-(Trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

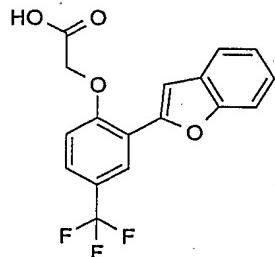
¹H NMR DMSO-d₆: δ 7.69 (1H, d), 7.60 (3H, m), 7.41 (3H, m), 7.20 (1H, d), 4.88 (2H, s)

MS: APCI (-ve) 295 (M-1)

Example 77

[2-(2-Benzofuranyl)-4-(trifluoromethyl)phenoxy]- acetic acid

20



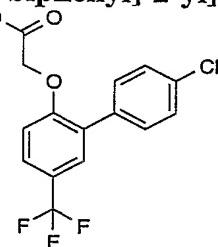
¹H NMR DMSO-d₆: δ 8.24 (1H, s), 7.85 (1H, s), 7.75 (1H, d), 7.70 (2H, d), 7.33 (3H, m), 5.07 (2H, s)

MS: APCI (-ve) 335 (M-1)

5

Example 78

[[4'-Chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



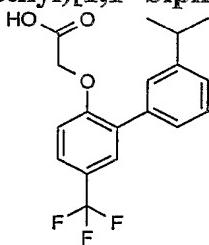
¹H NMR DMSO-d₆: δ 7.70 (1H, d), 7.64 (1H, d), 7.62 (1H, s), 7.62 (1H, d), 7.50 (1H, d),

10 7.50 (1H, d), 7.21 (1H, d), 4.81 (2H, s)

MS: APCI (-ve) 329/331 (M-1)

Example 79

[[3'-(1-Methylethyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

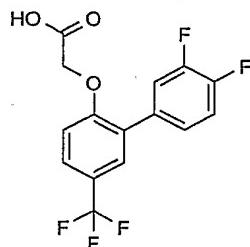
¹H NMR DMSO-d₆: δ 7.67 (1H, d), 7.57 (1H, s), 7.48 (1H, s), 7.38 (1H, t), 7.36 (1H, d), 7.25 (1H, d), 7.20 (1H, d), 4.85 (2H, s)

MS: APCI (-ve) 337 (M-1)

20

Example 80

[[3',4'-Difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



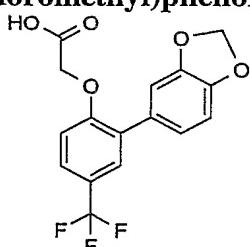
¹H NMR DMSO-d₆: δ 7.76 (1H, d), 7.71 (1H, d), 7.65 (1H, s), 7.51 (1H, d), 7.48 (1H, s), 7.25 (1H, d), 4.89 (2H, s)

MS: APCI (-ve) 331 (M-1)

5

Example 81

[2-(1,3-Benzodioxol-5-yl)-4-(trifluoromethyl)phenoxy]- acetic acid



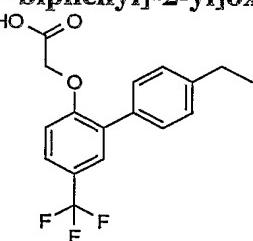
¹H NMR DMSO-d₆: δ 7.63 (1H, d), 7.57 (1H, s), 7.22 (1H, s), 7.16 (1H, d), 7.05 (1H, d),

10 6.98 (1H, d), 6.04 (2H, s), 4.83 (2H, s)

MS: APCI (-ve) 339 (M-1)

Example 82

[[4'-Ethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d₆: δ 7.66 (1H, d), 7.58 (1H, s), 7.51 (2H, d), 7.27 (2H, d), 7.18 (1H, d), 4.86 (2H, s), 2.65 (2H, q), 1.22 (3H, t)

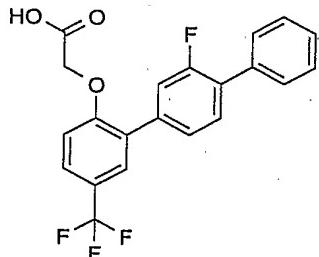
15 MS: APCI (-ve) 323 (M-1)

20

Example 83

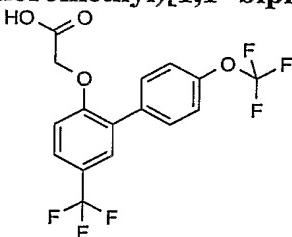
[[3'-Fluoro-5-(trifluoromethyl)[1,1':4',1"-terphenyl]-2-yl]oxy]- acetic acid

70

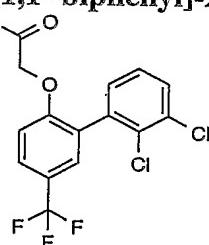


¹H NMR DMSO-d₆: δ 7.74 (1H, d), 7.65 (2H, m), 7.60 (1H, m), 7.59 (2H, m), 7.58 (1H, m), 7.52 (2H, m), 7.43 (1H, m), 7.12 (1H, m), 4.51 (2H, s)
 MS: APCI (-ve) 389 (M-1)

5

Example 84**[[4'-(Trifluoromethoxy)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yloxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.82 (2H, d), 7.62 (1H, d), 7.58 (1H, s), 7.41 (2H, d), 7.05 (1H, d),
 10 4.39 (2H, s)
 MS: APCI (-ve) 379 (M-1)

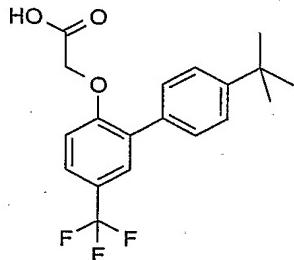
Example 85**[[2',3'-Dichloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yloxy]- acetic acid**

15

¹H NMR DMSO-d₆: δ 7.68 (1H, d), 7.66 (1H, d), 7.47 (1H, d), 7.48 (1H, s), 7.41 (1H, t),
 7.05 (1H, d), 4.26 (2H, d)
 MS: APCI (-ve) 363 (M-1)

20

Example 86**[[4'-(1,1-Dimethylethyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yloxy]- acetic acid**



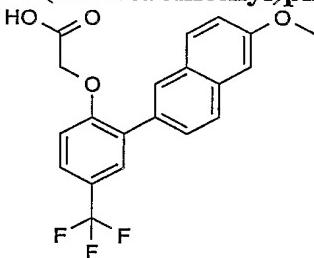
¹H NMR DMSO-d₆: δ 7.59 (1H, d), 7.57 (2H, d), 7.51 (1H, s), 7.44 (2H, d), 7.04 (1H, d), 4.47 (2H, s)

MS: APCI (-ve) 351 (M-1)

5

Example 87

[2-(6-Methoxy-2-naphthalenyl)-4-(trifluoromethyl)phenoxy]- acetic acid



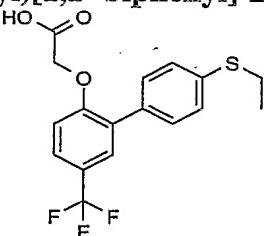
¹H NMR DMSO-d₆: δ 8.07 (1H, s), 7.87 (1H, d), 7.85 (2H, s), 7.62 (2H, d), 7.34 (1H, s),

10 7.17 (1H, d), 7.08 (1H, d), 4.41 (2H, s)

MS: APCI (-ve) 375 (M-1)

Example 88

[[4'-(Ethylthio)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

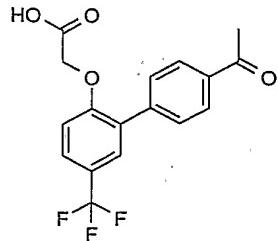
¹H NMR DMSO-d₆: δ 7.61 (2H, d), 7.59 (1H, d), 7.52 (1H, s), 7.35 (2H, d), 7.07 (1H, d), 4.50 (2H, s), 3.02 (2H, q), 1.27 (3H, t)

MS: APCI (-ve) 355 (M-1)

20

Example 89

[[4'-Acetyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



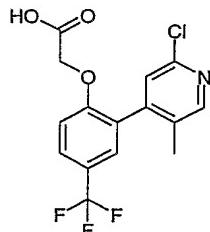
¹H NMR DMSO-d₆: δ 8.02 (2H, d), 7.77 (2H, d), 7.64 (1H, s), 7.72 (1H, d), 7.23 (1H, d), 4.83 (2H, s), 2.63 (3H, s)

MS: APCI (-ve) 337 (M-1)

5

Example 90

[2-(2-Chloro-5-methyl-4-pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid, ammonium salt

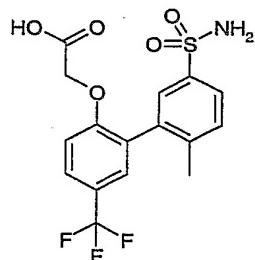


¹⁰ ¹H NMR DMSO-d₆: δ 8.30 (1H, d), 7.75 - 7.66 (1H, m), 7.49 (1H, d), 7.04 (2H, d), 4.28 (2H, s), 2.15 (3H, s)

MS:APCI (-ve) 449 (M-1)

Example 91

[[5'-(Aminosulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid, ammonium salt

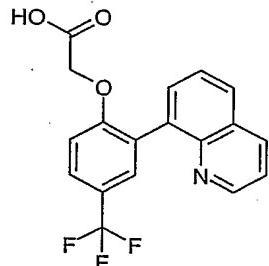


¹⁵ ¹H NMR DMSO-d₆: δ 7.73 - 7.65 (3H, m), 7.63 (1H, d), 7.44 (1H, d), 7.37 (1H, d), 7.01 (1H, d), 4.23 (2H, s), 2.24 (3H, s)

MS:APCI (-ve) 388 (M-1)

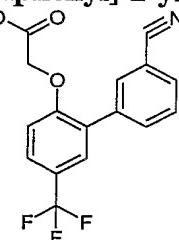
Example 92

[2-(8-Quinolinyl)-4-(trifluoromethyl)phenoxy]- acetic acid, ammonium salt



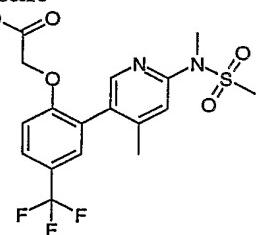
¹H NMR CDCl₃: δ 8.85 - 8.82 (1H, m), 8.33 - 8.29 (1H, m), 7.95 - 7.91 (1H, m), 7.82 - 7.78 (1H, m), 7.68 - 7.58 (3H, m), 7.50 - 7.46 (1H, m), 7.14 - 7.10 (1H, m), 4.54 (2H, s)
 MS:APCI (-ve) 346 (M-1)

5

Example 93**[[3'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid, ammonium salt**

¹H NMR CDCl₃: δ 8.00 (1H, d), 7.87 - 7.83 (1H, m), 7.66 - 7.52 (4H, m), 6.99 (1H, d),
 10 4.68 (2H, s)
 MS:APCI (-ve) 320 (M-1)

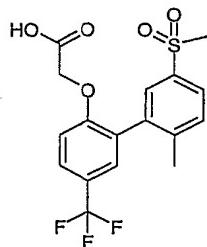
15

Example 94**[2-[4-Methyl-6-[methyl(methylsulfonyl)amino]-3-pyridinyl]-4-(trifluoromethyl)phenoxy]- acetic acid, ammonium salt**

¹H NMR DMSO-d6: δ 8.20 (1H, s), 7.71 (1H, m), 7.51 - 7.47 (1H, m), 7.33 (1H, s), 7.09 (1H, d), 4.52 (2H, s), 3.32 (3H, s), 3.18 (3H, d), 2.21 (3H, s)
 MS:APCI (-ve) 419 (M-1)

20

Example 95**[[2'-Methyl-5'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid, ammonium salt**



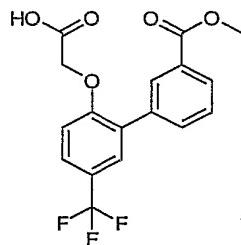
¹H NMR DMSO-d₆: δ 7.83 - 7.80 (1H, m), 7.74 - 7.69 (2H, m), 7.55 (1H, d), 7.49 (1H, d), 7.09 (1H, d), 4.46 (2H, s), 3.23 (3H, s), 2.26 (3H, s)

MS:APCI (+ve) 406 (M+1)

5

Example 96

2'-(Carboxymethoxy)-5'-(trifluoromethyl)-[1,1'-biphenyl]-3-carboxylic acid, 3-methyl ester

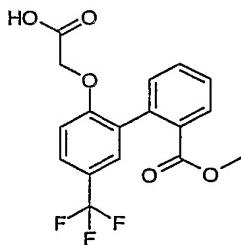


¹⁰ ¹H NMR DMSO-d₆: δ 8.15 - 8.13 (1H, m), 7.99 - 7.93 (2H, m), 7.68 - 7.55 (3H, m), 7.10 (1H, d), 4.46 (2H, s), 3.87 (3H, s)

MS:APCI (-ve) 353 (M-1)

Example 97

¹⁵ **2'-(Carboxymethoxy)-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid, 2-methyl ester**

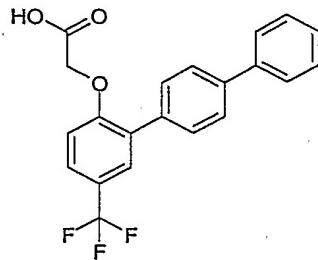


¹H NMR DMSO-d₆: δ 7.77 (1H, M), 7.66 - 7.59 (2H, m), 7.51 - 7.42 (3H, m), 4.23 (2H, s), 3.59 (4H, s)

²⁰ MS:APCI (-ve) 353 (M-1)

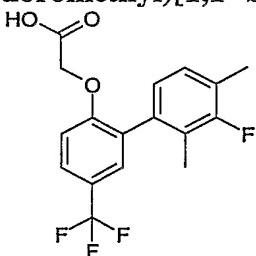
Example 98

[[5-(Trifluoromethyl)[1,1':4',1"-terphenyl]-2-yl]oxy]-acetic acid

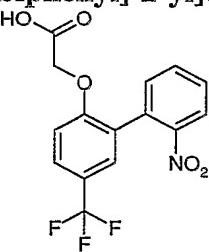


¹H NMR DMSO-d₆: δ 7.75 - 7.62 (7H, m), 7.53 - 7.46 (3H, m), 7.42 - 7.35 (1H, m), 7.21 - 7.15 (1H, m), 4.76 (2H, s)
MS:APCI (-ve) 371 (M-1)

5

Example 99**[[3'-Fluoro-2',4'-dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.66 - 7.62 (1H, m), 7.55 (1H, d), 7.34 (2H, d), 7.16 (1H, d), 4.78 (2H, s), 2.25 (6H, d)
MS:APCI (-ve) 341 (M-1)

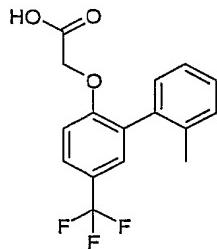
Example 100**[[2'-Nitro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid, ammonium salt**

15

¹H NMR DMSO-d₆: δ 8.00 (1H, m), 7.83 - 7.76 (1H, m), 7.70 - 7.55 (4H, m), 6.94 (1H, d), 4.08 (2H, s)
MS:APCI (-ve) 340 (M-1)

20

Example 101**[[2'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**



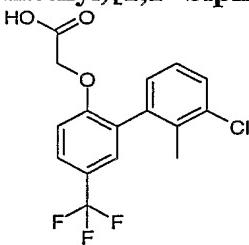
¹H NMR DMSO-d₆: δ 7.65 - 7.61 (1H, m), 7.34 - 7.32 (1H, m), 7.28 - 7.14 (4H, m), 7.02 - 6.98 (1H, m), 4.36 (2H, s), 2.13 (3H, s)

MS:APCI (-ve) 340 (M-1)

5

Example 102

[[3'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



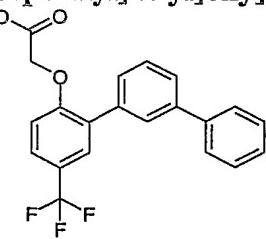
¹H NMR DMSO-d₆: δ 7.72 - 7.66 (1H, m), 7.47 - 7.40 (2H, m), 7.30 - 7.22 (1H, m), 7.18 -

10 7.14 (1H, m), 7.10 - 7.06 (1H, m), 4.56 (2H, s), 2.14 (3H, s)

MS:APCI (-ve) 343 (M-1)

Example 103

[[5-(Trifluoromethyl)[1,1':3',1"-terphenyl]-2-yl]oxy]- acetic acid



15

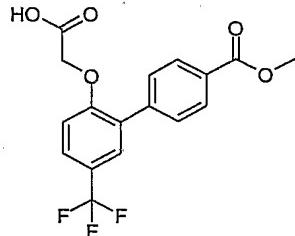
¹H NMR DMSO-d₆: δ 7.92 (1H, t), 7.76 - 7.72 (2H, m), 7.68 - 7.59 (4H, m), 7.56 - 7.34 (4H, m), 7.19 - 7.15 (1H, m), 4.69 (2H, s)

MS:APCI (-ve) 371 (M-1)

20

Example 104

2'-(Carboxymethoxy)-5'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxylic acid, 4-methyl ester



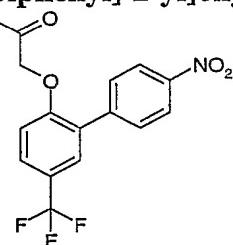
¹H NMR DMSO-d₆: δ 8.03 - 7.99 (2H, m), 7.82 - 7.79 (2H, m), 7.70 - 7.66 (1H, m), 7.63 - 7.61 (1H, m), 7.17 - 7.14 (1H, m), 4.62 (2H, s), 3.88 (3H, s)

MS:APCI (-ve) 353 (M-1)

5

Example 105

[[4'-Nitro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d₆: δ 8.30 - 8.26 (2H, m), 7.99 - 7.94 (2H, m), 7.75 - 7.67 (2H, m), 7.20

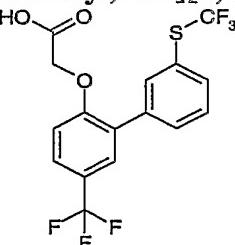
10

(1H, d), 4.65 (2H, s)

MS:APCI (-ve) 340 (M-1)

Example 106

[[5-(Trifluoromethyl)-3'-[(trifluoromethyl)thio][1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

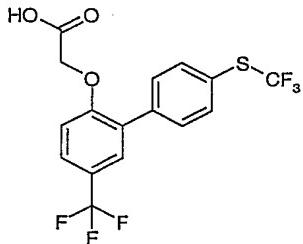
¹H NMR DMSO-d₆: δ 8.05 (1H, s), 7.91 - 7.87 (1H, m), 7.74 - 7.58 (4H, m), 7.17 (1H, d), 4.64 (2H, s)

MS:APCI (-ve) 395 (M-1)

20

Example 107

[[5-(Trifluoromethyl)-4'-[(trifluoromethyl)thio][1,1'-biphenyl]-2-yl]oxy]- acetic acid



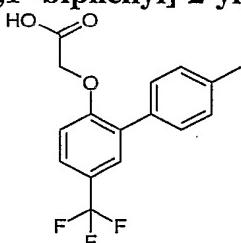
¹H NMR DMSO-d₆: δ 7.79 (4H, s), 7.76 - 7.72 (1H, m), 7.69 - 7.67 (1H, m), 7.25 (1H, d), 4.89 (2H, s)

MS:APCI (-ve) 395 (M-1)

5

Example 108

[[4'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



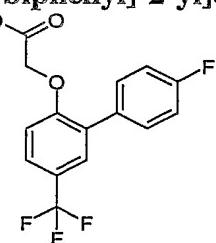
¹H NMR DMSO-d₆: δ 7.67 - 7.63 (1H, m), 7.57 - 7.54 (1H, m), 7.51 - 7.47 (2H, m), 7.25

10 (2H, d), 7.17 (1H, d), 4.82 (2H, s), 2.35 (3H, s)

MS:APCI (-ve) 309 (M-1)

Example 109

[[4'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d₆: δ 7.71 - 7.58 (4H, m), 7.31 - 7.18 (3H, m), 4.86 (2H, s)

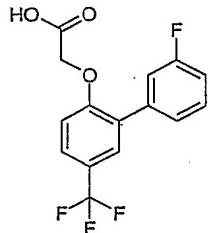
15 MS:APCI (-ve) 314 (M-1)

15

Example 110

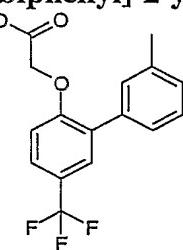
[[3'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

20



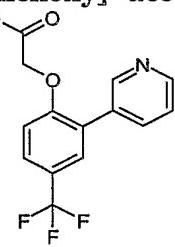
¹H NMR DMSO-d₆: δ 7.74 - 7.69 (1H, m), 7.66 - 7.64 (1H, m), 7.53 - 7.42 (3H, m), 7.26 - 7.18 (2H, m), 4.88 (2H, s)
MS:APCI (-ve) 314 (M-1)

5

Example 111**[[3'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR DMSO-d₆: δ 7.70 - 7.63 (1H, m), 7.56 (1H, d), 7.42 - 7.28 (3H, m), 7.21 - 7.15 (2H, m), 4.82 (2H, s), 2.34 (3H, s)
MS:APCI (-ve) 309 (M-1)

10

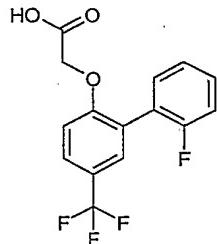
Example 112**[2-(3-Pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid**

15

¹H NMR DMSO-d₆: δ 8.88 (1H, s), 8.56 - 8.53 (1H, m), 8.15 - 8.09 (1H, m), 7.68 - 7.60 (2H, m), 7.48 - 7.42 (1H, m), 7.10 (1H, d), 4.43 (2H, s)
MS:APCI (+ve) 298 (M+1)

20

Example 113**[[2'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**



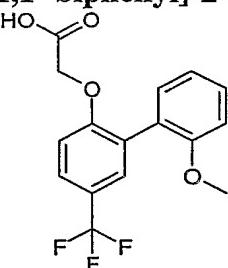
¹H NMR DMSO-d₆: δ 8.02 (1H, d), 7.92 - 7.90 (1H, m), 7.79 - 7.54 (4H, m), 7.28 (1H, d), 4.90 (2H, s)

MS:APCI (-ve) 313 (M-1)

5

Example 114

[[2'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



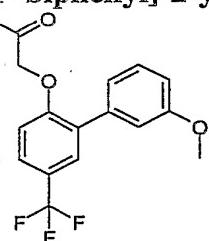
¹H NMR DMSO-d₆: δ 7.59 (1H, d), 7.42 (1H, s), 7.37 - 7.30 (2H, m), 7.11 - 6.95 (3H, m),

10 4.42 (2H, s), 3.72 (3H, s)

MS:APCI (-ve) 325 (M-1)

Example 115

[[3'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

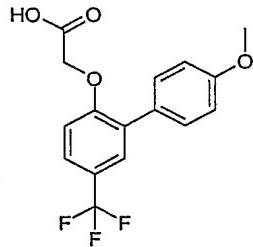
¹H NMR DMSO-d₆: δ 7.62 (1H, d), 7.56 - 7.54 (1H, m), 7.34 (1H, t), 7.27 - 7.25 (1H, m), 7.16 (1H, d), 7.11 (1H, d), 6.95 - 6.90 (1H, m), 4.56 (2H, s), 3.79 (3H, s)

MS:APCI (-ve) 325 (M-1)

20

Example 116

[[4'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



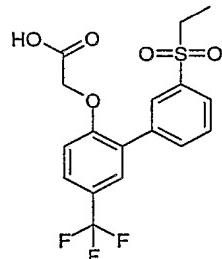
¹H NMR DMSO-d₆: δ 7.62 - 7.54 (4H, m), 7.04 (1H, d), 6.98 (2H, d), 4.45 (2H, s), 3.79 (3H, s)

MS:APCI (-ve) 325 (M-1)

5

Example 117

[[3'-(Ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



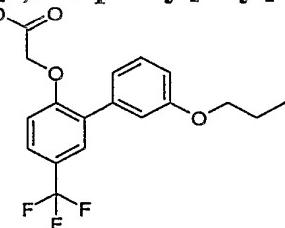
¹H NMR DMSO-d₆: δ 8.19 - 8.17 (1H, m), 8.11 - 8.07 (1H, m), 7.87 - 7.83 (1H, m), 7.73 -

10 7.64 (3H, m), 7.11 (1H, d), 4.39 (2H, s), 3.38 (2H, q), 1.14 (3H, t)

MS:APCI (-ve) 387 (M-1)

Example 118

[[3'-Propoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



¹H NMR DMSO-d₆: δ 7.70 - 7.65 (1H, m), 7.59 (1H, d), 7.33 (1H, t), 7.22 - 7.10 (3H, m),

15 6.95 - 6.91 (1H, m), 4.86 (2H, s), 3.97 (2H, t), 1.79 - 1.68 (2H, m), 0.98 (3H, t)

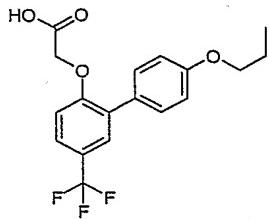
MS:APCI (-ve) 353 (M-1)

15

20

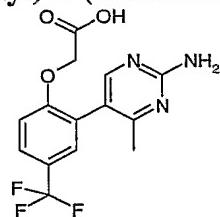
Example 119

[[4'-Propoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

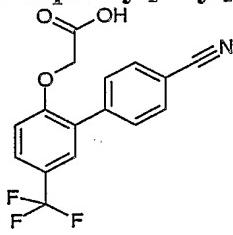


¹H NMR DMSO-d₆: δ 7.65 - 7.61 (1H, m), 7.56 - 7.50 (3H, m), 7.16 (1H, d), 7.01 - 6.96 (2H, m), 4.85 (2H, s), 3.97 (2H, t), 1.80 - 1.70 (2H, m), 0.99 (3H, t)
MS:APCI (-ve) 353 (M-1)

5

Example 120**[2-(2-Amino-4-methyl-5-pyrimidinyl)-4-(trifluoromethyl)phenoxy]- acetic acid**

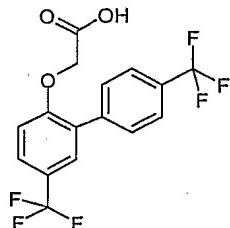
¹H NMR DMSO-d₆: δ 7.99 (s, 1H), 7.62 (dd, 1H), 7.43 (d, 1H), 7.01 (d, 1H), 6.56 (s, 2H), 4.41 (s, 2H), 2.15 (s, 3H).
MS:APCI (+ve) 328

Example 121**[[4'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**

¹H NMR CD₃OD: δ 7.86 - 7.73 (m, 4H), 7.65 (dd, 1H), 7.60 (d, 1H), 7.14 (d, 1H), 4.66 (s, 2H)
MS:APCI (+ve) 320

20

Example 122**[[4',5-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid**



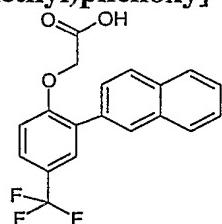
¹H NMR DMSO-d₆: δ 7.90 (2H, d), 7.78 (2H, d), 7.67 (1H, d), 7.62 (1H, s), 7.10 (1H, d), 4.47 (2H, s)

MS: APCI (-ve) 363 (M-1)

5

Example 123

[2-(2-Naphthalenyl)-4-(trifluoromethyl)phenoxy]- acetic acid



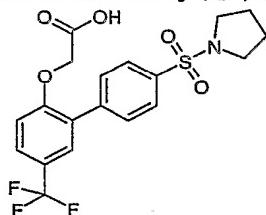
¹H NMR DMSO-d₆: δ 8.15 (1H, s), 7.93 (4H, m), 7.67 (1H, s), 7.64 (1H, d), 7.53 (2H, m),

10 7.09 (1H, d), 4.44 (2H, s)

MS: APCI (-ve) 345 (M-1)

Example 124

[[4'-(1-Pyrrolidinylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



15

(i) 1-[(4-Bromophenyl)sulfonyl]- pyrrolidine

A solution of 4-bromobenzenesulphonyl chloride (0.5g) and pyrrolidine (0.284g) in acetonitrile (5ml) were stirred at RT for 48h then partitioned between ethylacetate and water. The organics were separated, washed with water, dried and evaporated under reduced pressure. The residue was triturated with isohexane and filtered, yield 0.5g.

20

¹H NMR CDCl₃: δ 7.72-7.65 (4H, m); 3.28-3.21 (4H, m); 1.84-1.76 (4H, m)

(ii) [[4'-(1-Pyrrolidinylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

The title compound was prepared by the method of example 44, yield 0.13g.

25

¹H NMR CD₃OD: δ 7.83 - 7.75 (m, 4H), 7.56 - 7.52 (m, 1H), 7.50 (d, 1H), 7.01 (d, 1H), 4.46 (s, 2H), 3.20 - 3.14 (m, 4H), 1.72 - 1.65 (m, 4H).
MS:APCI (-ve) 428.

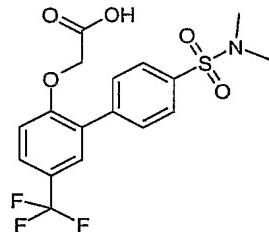
5

Example 125-134

The following compounds were synthesised in an analogous method to example 124

Example 125

10 [[4'-(Dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



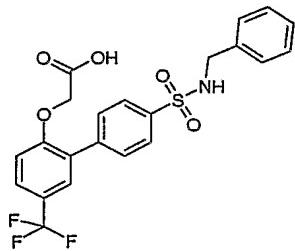
¹H NMR CD₃OD: δ 7.92 - 7.81 (m, 4H), 7.67 - 7.61 (m, 2H), 7.14 (d, 1H), 4.64 (s, 2H), 2.73 (s, 6H).

15

MS:APCI (+ve) 402

Example 126

[[4'-[[(Phenylmethyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



20

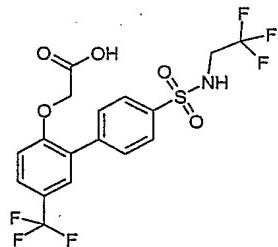
¹H NMR CD₃OD: δ 7.92 - 7.77 (m, 4H), 7.68 (d, 1H), 7.62 (s, 1H), 7.29 - 7.14 (m, 6H), 4.73 (s, 2H), 4.13 (s, 2H).

MS:APCI (-ve) 464.

25

Example 127

[[4'-[[(2,2,2-Trifluoroethyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



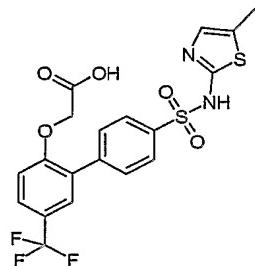
¹H NMR CD₃OD: δ 7.93 - 7.79 (m, 4H), 7.64 (d, 1H), 7.59 (d, 1H), 7.12 (d, 1H), 4.64 (s, 2H), 3.63 (t, 2H).

MS:APCI (-ve) 456

5

Example 128

[[4'-[[(5-Methyl-2-thiazolyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

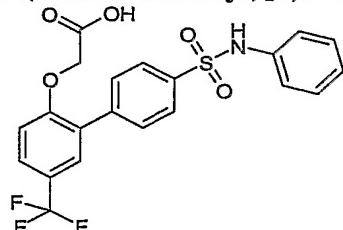


¹H NMR CD₃OD: δ 7.97 - 7.92 (m, 2H), 7.82 - 7.78 (m, 2H), 7.67 - 7.61 (m, 1H), 7.61 - 7.58 (m, 1H), 7.12 (d, 2H), 6.82 (d, 1H), 4.61 (s, 2H), 2.27 (d, 3H).

MS:APCI (-ve) 471

Example 129

[[4'-[{(Phenylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



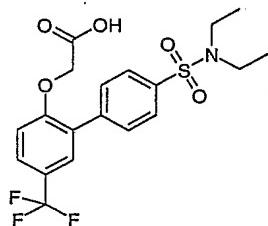
¹H NMR CD₃OD: δ 7.81 - 7.73 (m, 4H), 7.60 (dd, 1H), 7.54 (d, 1H), 7.25 - 7.02 (m, 6H), 4.55 (s, 2H).

MS:APCI (-ve) 450.

20

Example 130

[[4'-[{(Diethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



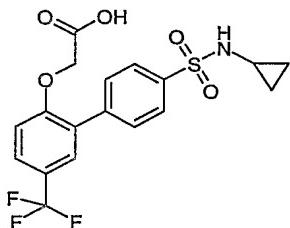
¹H NMR CD₃OD: δ 7.85 (s, 4H), 7.63 (dd, 1H), 7.59 (d, 1H), 7.11 (d, 1H), 4.58 (s, 2H), 3.27 (q, 4H), 1.16 (t, 6H).

MS:APCI (-ve) 450.

5

Example 131

[[4'-(Cyclopropylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

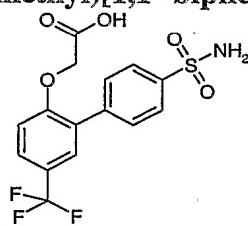


¹H NMR CD₃OD: δ 7.95 - 7.84 (m, 4H), 7.64 (dd, 1H), 7.61 (d, 1H), 7.12 (d, 1H), 4.61 (s, 2H), 2.23 - 2.16 (m, 1H), 0.58 - 0.53 (m, 4H).

MS:APCI (-ve) 414.

Example 132

[[4'-(Aminosulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



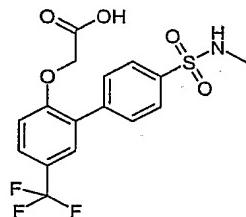
¹H NMR CD₃OD: δ 7.94 (d, 2H), 7.81 (d, 2H), 7.63 (dd, 1H), 7.58 (d, 1H), 7.12 (d, 1H), 4.60 (s, 2H).

MS:APCI (-ve) 374.

20

Example 133

[[4'-(Methylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid



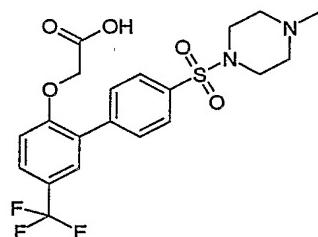
¹H NMR CD₃OD: δ 7.80 - 7.74 (m, 4H), 7.53 (dd, 1H), 7.50 (d, 1H), 4.48 (s, 2H), 2.47 (s, 3H).

MS:APCI (-ve) 388

5

Example 134

[[4'-(4-Methyl-1-piperazinyl)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yloxy]-acetic acid

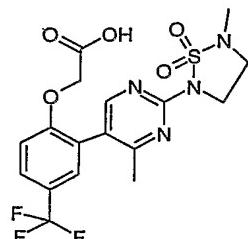


¹⁰ ¹H NMR CD₃OD: δ 7.85 - 7.70 (m, 4H), 7.55 - 7.51 (m, 1H), 7.49 (d, 1H), 7.00 (d, 1H), 4.41 (s, 2H), 3.03 - 2.95 (m, 4H), 2.48 (t, 4H), 2.21 (s, 3H).

MS:APCI (-ve) 457

Example 135

¹⁵ [2-[4-Methyl-2-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid



(i) 2,5-Dibromo-4-methyl-pyrimidine

Isoamyl nitrite (21ml) was added to a stirred suspension of 5-bromo-4-methyl-2-pyrimidinamine (1.75g) in bromoform (30ml) and the mixture heated at 85°C for 4h. After cooling, isohexane (300ml) was added and the solution passed through a pad of silica-gel. The silica was washed with petrol (1000ml), dichloromethane (200ml) then the product eluted with ethylacetate. The ethylacetate layer was evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 5% diethylether/isohexane, yield 0.9g

¹H NMR CDCl₃: δ 8.52 (s, 1H), 2.64 (s, 3H)

MS:APCI (-ve) 249/51/53

5 (ii) 5-Bromo-4-methyl-2-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)- pyrimidine
Sodium hydride (0.128g, 60% disp. in oil) was added to a stirred solution of 2-methyl-
1,2,5-thiadiazolidine 1,1-dioxide (0.433g) in THF (10ml). DMF (10ml) was added and the
mixture heated at 80°C for 5min then a solution of the product from step (i) (0.8g) in DMF
(5ml) was added. The mixture was heated at 60°C for 10min, poured into water (100ml),
10 acidified with citric acid and extracted with ethylacetate. The organics were evaporated
under reduced pressure and the residue purified by chromatography on silica eluting with
diethylether, yield 0.58g.

15 ¹H NMR CDCl₃: δ 8.50 (s, 1H), 4.05 (t, 2H), 3.45 (t, 2H), 2.87 (s, 3H), 2.58 (s, 3H).
MS:APCI (+ve) 307/9

20 (iii) [2-[4-Methyl-2-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)-5-pyrimidinyl]-
4-(trifluoromethyl)phenoxy]- acetic acid

The title compound was prepared by the method of example 44, yield 0.05g.

25 ¹H NMR CDCl₃: δ 8.34 (s, 1H), 7.47 (dd, 1H), 7.32 (d, 1H), 6.90 (d, 1H), 4.36 (s, 2H),
4.05 (t, 2H), 3.40 (t, 4H), 2.77 (s, 3H), 2.27 (s, 3H).
MS:APCI (+ve) 447

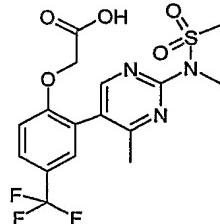
25 Example 136-137

The following compounds were synthesised in an analogous method to example 135

Example 136

[2-[4-Methyl-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-4-

30 (trifluoromethyl)phenoxy]- acetic acid

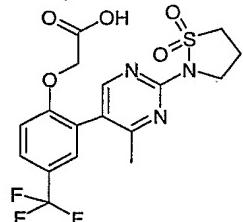


¹H NMR CDCl₃: δ 8.37 (s, 1H), 7.63 (dd, 1H), 7.40 (d, 1H), 6.96 (d, 1H), 4.60 (s, 2H),
3.57 (s, 3H), 3.53 (s, 3H), 2.40 (s, 3H).

MS:APCI (-ve) 418

Example 137

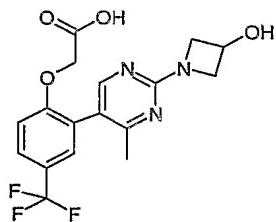
[2-[2-(1,1-Dioxido-2-isothiazolidinyl)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid, ammonium salt



⁵ ^1H NMR CDCl₃: δ 8.37 (s, 1H), 7.60 (dd 1H), 7.36 (d, 1H), 7.02 (d, 1H), 4.53 (s, 2H), 4.09 (t, 2H), 3.49 (t, 2H), 2.51 (quintet, 2H), 2.39 (s, 3H).
MS:APCI (+ve) 432.

Example 138

[2-[2-(3-Hydroxy-1-azetidinyl)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-acetic acid



(i) 1-(5-Bromo-4-methyl-2-pyrimidinyl)- 3-azetidinol

¹⁵ A mixture of the product from example 135 step (i) (0.75g), azetidin-3-ol hydrochloride (0.66g) and triethylamine (0.9ml) in ethanol (10ml) was stirred at RT for 2h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica eluting with 60% diethylether/isohexane as eluant, yield 0.7g.

²⁰ ^1H NMR CDCl₃: δ 8.22 (s, 1H), 4.78 - 4.72 (m, 1H), 4.40 - 4.33 (m, 2H), 3.99 - 3.93 (m, 2H), 2.45 (s, 3H)

(ii) [2-[2-(3-Hydroxy-1-azetidinyl)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy] - acetic acid

²⁵ The title compound was prepared in an analogous method to example 44, yield 0.04g.

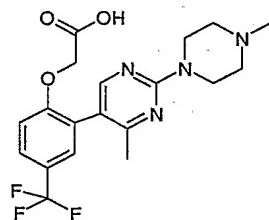
^1H NMR CD₃OD: δ 8.09 (s, 1H), 7.64 (m, 1H), 7.43 (d, 1H), 7.08 (d, 1H), 4.71 - 4.64 (m, 1H), 4.61 (s, 2H), 4.41 - 4.34 (m, 2H), 3.96 - 3.91 (m, 2H), 2.25 (s, 3H).
MS:APCI (+ve) 384

Example 139-141

The following compounds were synthesised in an analogous method to example 138

Example 139

- 5 [2-[4-Methyl-2-(4-methyl-1-piperazinyl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-acetic acid

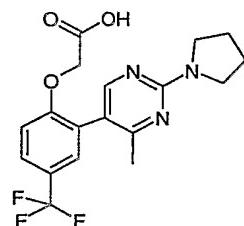


¹H NMR CDCl₃: δ 8.19 (s, 1H), 7.57 (d, 1H), 7.38 (d, 1H), 6.99 (d, 1H), 4.51 (s, 2H), 4.3-3.8 (br s, 4H), 3-2.8 (br s, 4H), 2.63 (s, 3H), 2.29 (s, 3H).

10 MS:APCI (+ve) 411

Example 140

- [2-[4-Methyl-2-(1-pyrrolidinyl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid

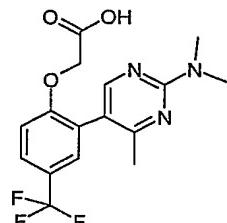


¹H NMR CD₃OD: δ 7.95 (s, 1H), 7.36 (d, 1H), 7.59 - 7.54 (m, 1H), 7.01 (d, 1H), 4.65 (s, 2H), 3.50 (t, 4H), 2.15 (s, 3H), 1.96 - 1.91 (m, 4H).

MS:APCI (+ve) 382

Example 141

- [2-[2-(Dimethylamino)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid

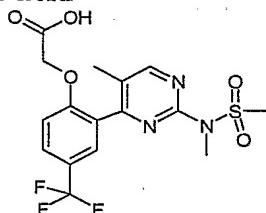


¹H NMR CD₃OD: δ 8.05 (s, 1H), 7.67 - 7.63 (m, 1H), 7.44 (d, 1H), 7.10 (d, 1H), 4.75 (s, 2H), 3.20 (s, 6H).

MS:APCI (+ve) 356

Example 142

[2-[5-Methyl-2-[methyl(methylsulfonyl)amino]-4-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid



5

(i) *N*-(4-Chloro-5-methyl-2-pyrimidinyl)-*N*-methyl-methanesulfonamide

A mixture of *N*-methylsulphonamide (3.35g), 2,4-dichloro-5-methyl pyrimidine (5g) and potassium carbonate (4.3g) in DMF (50ml) was heated at 80°C for 4h. The reaction was quenched with water (200ml) and extracted with ethylacetate. The organics were dried, evaporated under reduced pressure and the residue triturated with ether. The solid was filtered off (4-isomer) and the filtrate evaporated under reduced pressure and subjected to RPHPLC to obtain the 2-isomer, yield 0.37g.

¹H NMR CDCl₃: δ 8.35 (s, 1H), 3.51 (s, 3H), 3.48 (s, 3H), 2.29 (d, 3H).

15

(ii) *[2-[5-Methyl-2-[methyl(methylsulfonyl)amino]-4-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid*

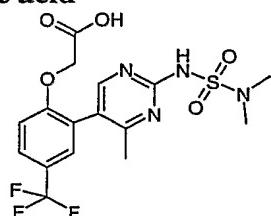
The title compound was prepared in an analogous method to example 44, yield 0.04g.

20 ¹H NMR CD₃OD: δ 8.50 (s, 1H), 7.16 (d, 1H), 7.74 (dd, 1H), 7.62 (d, 1H), 4.68 (s, 2H), 3.50 (s, 3H), 3.45 (s, 3H), 2.19 (s, 3H).

MS:APCI (+ve) 420

Example 143

25 **[2-[2-[(Dimethylamino)sulfonyl]amino]-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid**



(i) *N'*-(5-Bromo-4-methyl-2-pyrimidinyl)-*N,N*-dimethyl- sulfamide

A mixture of 5-bromo-4-methyl-2-pyrimidinamine (0.75g) and dimethylsulphonyl chloride (0.43ml) in pyridine (20ml) was heated at 80°C for 17h. The solvent was

removed under reduced pressure and the residue purified by chromatography on silica eluting with diethylether then ethylacetate. The residue was then purified by RPHPLC, yield 0.12g.

5 MS:APCI (-ve) 295/6

(ii) [2-[2-[(Dimethylamino)sulfonyl]amino]-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid

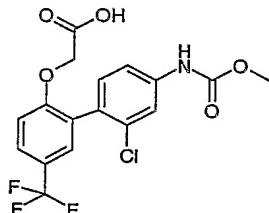
The title compound was prepared in an analogous method to example 44, yield 0.01g.

10 ^1H NMR CD₃OD: δ 8.27 (s, 1H), 7.68 (d, 1H), 7.49 (s, 1H), 7.11 (d, 1H), 4.70 (s, 2H), 2.98 (s, 6H), 2.32 (s, 3H).

MS:APCI (+ve) 435.

15 **Example 144**

[[2'-Chloro-4'-(methoxycarbonyl)amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yloxy]acetic acid



i) 2-Chloro-2'-(phenylmethoxy)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine

20 The product from example 32 step (ii) (0.5g) and 4-bromo-3-chloroaniline (0.38g) were dissolved in toluene (4ml). Ethanol (1ml), 2M aqueous sodium carbonate (1ml) and Pd(PPh₃)₄ (0.115g) were added sequentially and the mixture heated at reflux for 4h. The reaction was cooled, evaporated, dissolved in EtOAc, washed with water and brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography on silica eluting with 10% EtOAc/isohexane. Yield 0.23g.

25 ^1H NMR DMSO-d₆: δ 7.67 (ddd, 1H), 7.4 (d, 1H), 7.27-7.34 (m, 6H), 7.01 (d, 1H), 6.7 (d, 1H), 6.55 (dd, 1H), 5.47 (s, 2H) 5.18 (s, 2H)

ii) 4'-Amino-2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-ol

30 5% Pt/C (0.088g) was added to a solution of the product from step (i) in ethanol (20ml) and hydrogenated at RT and 1 bar for 18h. Extra Pt/C (0.1g) was added and hydrogenated for a further 3h at 2 bar. The catalyst was removed by filtration and the filtrate evaporated to leave a solid residue. The residue was purified by chromatography on silica eluting with 50% EtOAc/isohexane. Yield 0.083g.

¹H NMR DMSO-d6: δ 10.2 (s, 1H), 7.49 (d, 1H), 7.3 (d, 1H), 7.03 (d, 1H), 6.96 (d, 1H), 6.68 (d, 1H), 6.54 (dd, 1H), 5.44 (s, 2H)

iii) [[4'-Amino-2'-chloro-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl]oxy]acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 1 step (i) using the product from step (ii). Yield 0.07g. Used in step (iv) without characterisation.

iv) [[2'-Chloro-4'-(methoxycarbonyl)amino]-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl]oxy]acetic acid, 1,1-dimethylethyl ester

The product from step (iii) (0.07g) was dissolved in DCM (5ml), triethylamine (0.024ml) added, followed by methyl chloroformate (0.013ml) and stirred for 20h. Further triethylamine (0.024ml) and methyl chloroformate (0.013ml) were added three times over to achieve complete reaction. The solvent was removed by evaporation to give the crude product which was carried forward to step (v) without characterisation.

v) [[2'-Chloro-4'-(methoxycarbonyl)amino]-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl]oxy]acetic acid

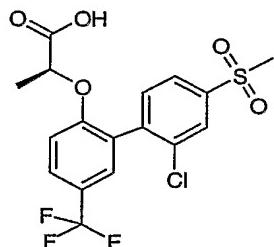
The title compound was prepared by the method of example 1 step (iii) using the product from step (iv).

¹H NMR DMSO-d6: δ 9.94 (s, 1H), 7.69 (dd, 2H), 7.41-7.47 (m, 2H), 7.35 (d, 1H), 7.13 (d, 1H), 4.65 (s, 2H), 3.7 (s, 3H)

MS:APCI (-ve) 402

Example 145

2-[[2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



i) 2-Chloro-1-iodo-4-(methylthio)benzene

Sodium methanethiolate (5g) was added to a solution of 4-fluoro-2-chloro-iodobenzene (18.3g) and stirred for 20h. The mixture was poured into water, extracted with ether, washed with brine, dried (MgSO₄) and evaporated. Yield 18.5g.

¹H NMR DMSO-d6: δ 7.81 (d, 1H), 7.43 (dd, 1H), 6.98 (dd, 1H), 3.32 (s, 3H)

ii) 2-Chloro-1-iodo-4-(methylsulfonyl)benzene

Mcpba (8.6g) was added portionwise to a stirred solution of the product from step (i) (5g) in DCM (100ml). After 1h, the reaction was diluted with DCM (200ml), washed with saturated aqueous sodium bicarbonate, dried (MgSO_4) and evaporated under reduced pressure. Yield 3.2g

^1H NMR DMSO-d6: δ 8.26 (d, 1H), 8.06 (d, 1H), 7.59 (dd, 1H), 3.32 (s, 3H)

iii) 2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl]oxy]methyl]benzene

The subtitle compound was prepared by the method of example 144 step (i) using the product from step (ii) and the product from example 32 step (ii). Yield 2.2g

^1H NMR DMSO-d6: δ 8.11 (s, 1H), 7.95 (dd, 1H), 7.82 (d, 1H), 7.72 (d, 1H), 7.61 (d, 1H), 7.41 (d, 1H), 7.27-7.36 (m, 5H), 5.25 (s, 2H), 3.35 (s, 3H)

iv) 2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)-[1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 144 step (ii) using the product from step (iii). Yield 0.95g

^1H NMR DMSO-d6: δ 10.72 (s, 1H), 8.08 (d, 1H), 7.93 (dd, 1H), 7.63-7.68 (m, 2H), 7.49 (d, 1H), 7.14 (d, 1H), 3.35 (s, 3H)

MS:APCI (-ve) 349

v) 2-[[2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-
(2S)- propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 32 step (v) using the product from step (iv) and tert-butyl R-lactate. Yield 0.25g.

^1H NMR DMSO-d6: δ 8.11 (d, 1H), 7.97 (d, 1H), 7.82 (dd, 1H), 7.73 (d, 1H), 7.62 (d, 1H), 7.15 (d, 1H), 5.0 (brs, 1H), 3.36 (s, 3H), 1.36-1.39 (m, 12H)

vi) 2-[[2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-
(2S)- propanoic acid

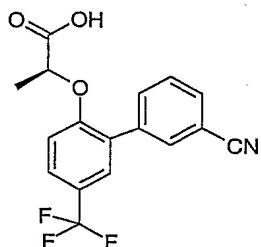
The title compound was prepared by the method of example 1 step (iii) using the product from step (v). Yield 0.12g.

^1H NMR DMSO-d6: δ 8.09 (d, 1H), 7.95 (dd, 1H), 7.82 (s, 1H), 7.76 (dd, 1H), 7.58 (d, 1H), 7.14 (d, 1H), 4.87 (q, 1H), 3.36 (s, 3H), 1.35 (d, 3H)

MS:APCI (-ve) 421

Example 146

2-[[3'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- (2S)-propanoic acid



i) 4,4,5,5-Tetramethyl-2-[2-(phenylmethoxy)-5-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane

Pinacol (1.82g) was added to a solution of the product from example 32 step (ii) (4.54g) in ether (40ml) and stirred at RT for 20h. The reaction was diluted with ether (100ml), washed with brine, dried ($MgSO_4$) and evaporated. Yield 5.7g.

1H NMR DMSO-d6: δ 7.82 (d, 1H), 7.79 (d, 1H), 7.6 (d, 2H), 7.4 (t, 2H), 7.32 (d, 1H), 7.27 (d, 1H), 5.24 (s, 2H), 1.32 (s, 12H)

ii) 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)phenol
10% Pd/C (0.5g) was added to a solution of the product from step (i) in EtOAc (80ml) and hydrogenated at RT and 1 bar for 1h, and for a further 3h at 3 bar. The catalyst was removed by filtration and the filtrate evaporated to leave a solid product. Yield 4.2g.

1H NMR DMSO-d6: δ 9.99 (d, 1H), 7.72 (s, 1H), 7.63 (d, 1H), 6.99 (d, 1H), 1.3 (d, 12H)

iii) 2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 32 step (v) using the product from step (ii) and tert-butyl R-lactate. Yield 4.0g. The crude material was carried forward to step (iv).

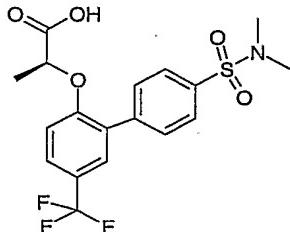
iv) 2-[2-Borono-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid
TFA (10ml) was added to a solution of the product from step (iii) (4.0g) in DCM (100ml) and stirred for 30min. The TFA was evaporated and the residue dissolved in a mixture of 1M hydrochloric acid (30ml) and acetonitrile (30ml). After 1h the mixture was evaporated to dryness, dissolved in 1M sodium hydroxide, washed with ether and adjusted to pH 2 with concentrated hydrochloric acid. The aqueous was then extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated. Yield 2.0g. The crude material was carried forward to step (v).

v) 2-[[3'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
The title compound was prepared by the method of example 144 step (i) using the product from step (iv) and 3-bromobenzonitrile.

¹H NMR DMSO-d₆: δ 8.13 (t, 1H), 8.01 (tdt, 1H), 7.85 (dt, 1H), 7.71-7.76 (m, 2H), 7.65 (dt, 1H), 7.17-7.2 (m, 1H), 5.11 (q, 1H), 1.47 (d, 3H)
 MS:APCI (-ve) 334

5 **Example 147**

2-[[4'--[Dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

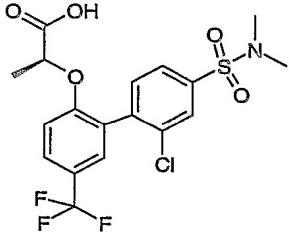


The title compound was prepared by the method of example 144 step (i) using the product
 10 from example 146 step (iv) and 4-bromo-N,N-dimethyl-benzenesulfonamide.

¹H NMR DMSO-d₆: δ 7.95 (d, 2H), 7.83 (d, 2H), 7.77 (d, 1H), 7.73 (s, 1H), 7.21 (d, 1H),
 5.14 (q, 1H), 2.69 (s, 6H), 1.51 (d, 3H)
 MS:APCI (-ve) 416

15 **Example 148**

2-[[2'-Chloro-4'--[dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



i) 3-Chloro-4-iodobenzenesulfonamide

A solution of sodium nitrite (3.27g) in water was added dropwise over 1h to a stirred
 20 solution of 3-chloro-4-iodoaniline (10.0g) in a mixture of THF (120ml) and concentrated
 hydrochloric acid (50ml) at -5 to -1°C. Magnesium chloride (6.39g) was then added and
 the resulting mixture poured into a stirred solution of acetic acid (50ml) saturated with
 sulfur dioxide and containing cuprous chloride (2.14g). After heating at 34°C for 30min,
 25 the mixture was poured into brine, extracted with EtOAc, washed with aqueous sodium
 bicarbonate and brine, dried (MgSO₄) and evaporated. The residue was dissolved in THF
 (100ml), 0.880 ammonia (100ml) added and stirred for 2h. The mixture was diluted with
 brine, extracted with EtOAc, washed with brine, dried (MgSO₄) and evaporated. The

residue was treated with isohexane/ether (4:1) and filtered to give the subtitle compound. Yield 5.67g.

¹H NMR DMSO-d6: δ 8.18 (d, 1H), 7.92 (d, 1H), 7.56 (s, 1H), 7.47 (dd, 1H)

5 ii) 3-Chloro-4-iodo-N,N-dimethylbenzenesulfonamide

Sodium hydride (0.33g) was added to a solution of the product from step (i) (1.2g) in DMF (25ml) and stirred for 20min. Methyl iodide (0.5ml) was added dropwise and then stirred for a further 1h. The reaction mixture was quenched with water, extracted with EtOAc, dried ($MgSO_4$) and evaporated. The residue was treated with ether to give to give the

10 subtitle compound as a white solid. Yield 0.45g.

¹H NMR DMSO-d6: δ 8.05 (d, 1H), 7.82 (d, 1H), 7.31 (dd, 1H), 2.75 (s, 6H)

15 iii) 2-[[2'-Chloro-4'-(dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

The title compound was prepared by the method of example 144 step (i) using the product from step (ii) and the product from example 146 step (iv).

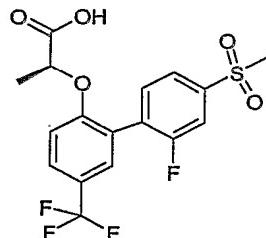
¹H NMR DMSO-d6: δ 7.86 (t, 1H), 7.75-7.79 (m, 3H), 7.61 (d, 1H), 7.14 (d, 1H), 4.88 (q, 1H), 2.7 (s, 6H), 1.35 (d, 3H)

MS:APCI (-ve) 450

20

Example 149

2-[[2'-Fluoro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



25 i) Trifluoromethanesulfonic acid, 2-fluoro-4-(methylsulfonyl)phenyl ester
2-Fluoro-4-(methylsulfonyl)phenol (1.44g) was dissolved in DCM (20ml), triethylamine (1.17ml) added, followed by trifluoromethanesulfonic anhydride (1.57ml) and stirred for 1h. The solution was washed with brine, dried ($MgSO_4$) and evaporated to give the subtitle compound.

30 ¹H NMR CDCl₃: δ 7.83-7.92 (m, 2H), 7.55-7.61 (m, 1H), 3.11 (s, 3H)

ii) 2-[[2'-Fluoro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)- propanoic acid

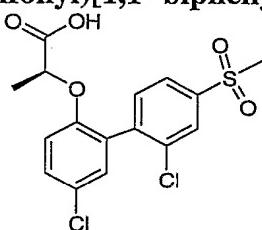
The title compound was prepared by the method of example 144 step (i) using the product from step (i) and the product from example 146 step (iv).

¹H NMR DMSO-d6: δ 7.79-7.9 (m, 3H), 7.74 (dd, 1H), 7.64 (s, 1H), 7.12 (d, 1H), 4.87 (q, 1H), 3.31 (s, 3H), 1.35 (d, 3H)

5 MS:APCI (-ve) 405

Example 150

[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



10 i) [[[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]methyl]benzene

The subtitle compound was prepared by the method of example 144 step (i) using the product from example 16 step (ii) and the product from example 145 step (ii). Yield 1.08g.

¹H NMR DMSO-d6: δ 8.09 (d, 1H), 7.94 (dd, 1H), 7.67 (d, 1H), 7.49 (dd, 1H), 7.22-7.34 (m, 7H), 5.14 (s, 2H), 3.35 (s, 3H)

15 ii) [[[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-ol

The subtitle compound was prepared by the method of example 144 step (ii) using the product from step (i). Yield 0.45g.

¹H NMR DMSO-d6: δ 10.04 (s, 1H), 8.06 (d, 1H), 7.91 (dd, 1H), 7.63 (d, 1H), 7.32 (dd, 1H), 7.2 (d, 1H), 6.97 (d, 1H), 3.34 (s, 3H)

iii) [[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 32 step (v) using the product from step (ii) and tert-butyl R-lactate. Yield 0.24g.

¹H NMR DMSO-d6: δ 8.09 (d, 1H), 7.95 (d, 1H), 7.7 (d, 1H), 7.48 (dd, 1H), 7.33 (d, 1H), 6.98 (d, 1H), 4.85 (brs, 1H), 3.35 (s, 3H), 1.37 (s, 9H), 1.32 (d, 3H)

iv) [[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

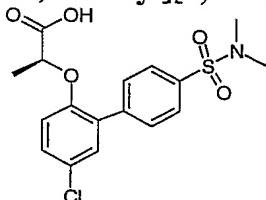
The title compound was prepared by the method of example 1 step (iii) using the product from step (iii). Yield 0.11g.

¹H NMR DMSO-d6: δ 8.07 (d, 1H), 7.92 (dd, 1H), 7.81 (s, 1H), 7.42 (dd, 1H), 7.28 (d, 1H), 6.97 (d, 1H), 4.65 (q, 1H), 3.35 (s, 3H), 1.29 (d, 3H)

MS:APCI (-ve) 387

Example 151

[[5-Chloro-4'-(dimethylamino)sulfonyl][1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



5

i) 2-[5-Chloro-2-(phenylmethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaboralane

The subtitle compound was prepared by the method of example 146 step (i) using the product from example 16 step (ii). Yield 3.3g.

^1H NMR DMSO-d6: δ 7.27-7.64 (m, 7H), 6.85 (d, 1H), 5.09 (s, 2H), 1.36 (s, 12H)

10

ii) 4-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

The subtitle compound was prepared by the method of example 146 step (ii) using the product from step (i). Purified by chromatography on silica eluting with 50% EtOAc/isohexane. Yield 1.89g.

15

^1H NMR DMSO-d6: δ 7.76-7.79 (s, 1H), 6.79-7.62 (m, 3H), 1.36 (s, 12H)

iii) 2-[4-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]-(2S)-propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 32 step (v) using the product from step (ii) and tert-butyl R-lactate. Yield 3.5g. The crude material was carried forward to step (iv).

iv) 2-(2-Borono-4-chlorophenoxy)-(2S)-propanoic acid

The subtitle compound was prepared by the method of example 146 step (iv) using the product from step (iii). Yield 2.5g. The crude material was carried forward to step (v).

v) [[5-Chloro-4'-(dimethylamino)sulfonyl][1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

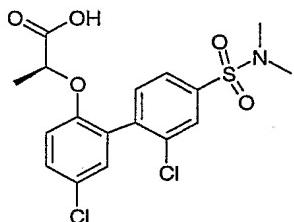
The title compound was prepared by the method of example 144 step (i) using the product from step (iv) and 4-bromo-N,N-dimethylbenzenesulfonamide and THF as solvent. Yield (0.068g).

^1H NMR DMSO-d6: δ 8.01 (d, 2H), 7.75 (d, 2H), 7.3-7.41 (m, 2H), 6.93 (d, 1H), 4.56 (bm, 1H), 2.65 (s, 6H), 1.33 (d, 3H)

MS:APCI (-ve) 382

Example 152

[[2',5-Dichloro-4'-(dimethylamino)sulfonyl][1,1'-biphenyl]-2-yl]oxy-(2S)-propanoic acid



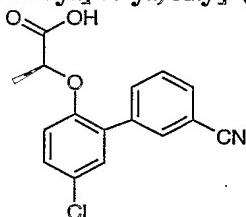
- 5 The title compound was prepared by the method of example 144 step (i) using the product from example 151 step (iv), the product from example 148 step (ii) and methanol as solvent. Yield (0.08g).

¹H NMR DMSO-d₆: δ 7.9 (bm, 1H), 7.82 (s, 1H), 7.74 (dd, 1H), 7.4 (dd, 1H), 7.26 (d, 1H), 6.92 (d, 1H), 4.34 (bm, 1H), 2.7 (s, 6H), 1.2 (d, 3H)

10 MS:APCI (-ve) 416

Example 153

[(5-Chloro-3'-cyano[1,1'-biphenyl]-2-yl)oxy-(2S)-propanoic acid



- 15 The title compound was prepared by the method of example 144 step (i) using the product from example 151 step (iv), 3-bromobenzenenitrile and THF as solvent.

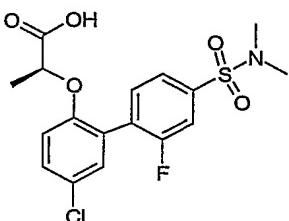
¹H NMR DMSO-d₆: δ 8.25 (s, 1H), 8.06 (d, 1H), 7.79 (d, 1H), 7.63 (t, 1H), 7.4 (d, 1H), 7.33 (dd, 1H), 6.95 (d, 1H), 4.64 (q, 1H), 1.32 (d, 3H)

MS:APCI (-ve) 300

20

Example 154

[[5-Chloro-4'-(dimethylamino)sulfonyl]-2'-fluoro[1,1'-biphenyl]-2-yl]oxy-(2S)-propanoic acid



- 25 i) 4-Bromo-N,N-dimethyl-3-fluorobenzenesulfonamide

The subtitle compound was prepared by the method of example 148 step (ii) using 4-bromo-3-fluorobenzenesulfonamide 1.14g.

- 5 ii) [[5-Chloro-4'-(dimethylamino)sulfonyl]-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

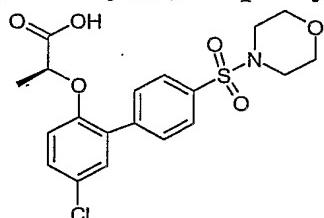
The title compound was prepared by the method of example 144 step (i) using the product from step (i), the product from example 151 step (iv) and THF as solvent.

¹H NMR DMSO-d₆: δ 7.94 (t, 1H), 7.58-7.62 (m, 2H), 7.35-7.4 (m, 2H), 6.93 (d, 1H), 4.48 (q, 1H), 2.7 (s, 6H), 1.26 (d, 3H)

10 MS:ESI (+ve) 402

Example 155

[[5-Chloro-4'-(4-morpholinylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



15 A mixture of the product from example 151 step (iv) (0.126g), sodium carbonate (0.22g), 4-[(4-bromophenyl)sulfonyl]morpholine (0.16g) and Pd(dppf)Cl₂ (0.03g) in dioxane (10ml) was heated under reflux for 4h. The mixture was evaporated and purified by RVHPLC (MeCN/aqNH₄Cl). Yield 0.09g.

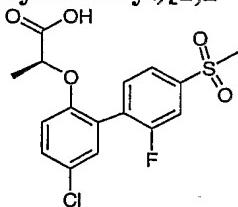
¹H NMR DMSO-d₆: δ 8.03 (d, 2H), 7.74 (d, 2H), 7.31-7.39 (m, 2H), 6.93 (d, 1H), 4.55

20 (m, 1H), 3.65 (m, 2H), 2.92 (m, 2H), 1.34 (d, 3H)

MS:APCI (-ve) 426

Example 156

[[5-Chloro-2'-fluoro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

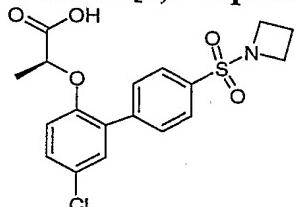


25

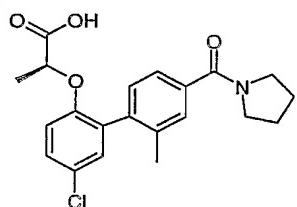
The title compound was prepared by the method of example 155 using the product from example 151 step (iv) and the product from example 149 step (i).

¹H NMR DMSO-d₆: δ 7.81-7.88 (m, 3H), 7.41-7.49 (m, 2H), 7.0 (d, 1H), 4.9 (q, 1H), 3.3 (s, 3H), 1.37 (d, 3H)

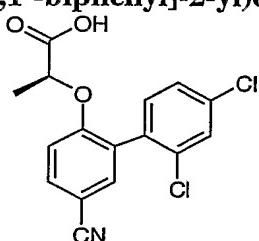
30 MS:ESI (-ve) 371

Example 157**2-[[4'-(1-Azetidinylsulfonyl)-5-chloro[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid**

- 5 The title compound was prepared by the method of example 144 step (i) using the product from example 151 step (iv), 1-[(4-bromophenyl)sulfonyl]azetidine and THF as solvent. Yield 0.028g.
- 10 ^1H NMR DMSO-d₆: δ 7.97 (d, 2H), 7.82 (d, 2H), 7.39-7.43 (m, 2H), 7.01 (d, 1H), 4.85 (m, 1H), 3.72 (t, 4H), 2.04 (q, 2H), 1.42 (d, 3H)
- MS:ESI (-ve) 394

Example 158**2-[[5-Chloro-2'-methyl-4'-(1-pyrrolidinylcarbonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid, sodium salt**

- 15 The title compound was prepared by the method of example 155 using the product from example 151 step (iv) and 1-(4-bromo-3-methylbenzoyl)pyrrolidine. Yield 0.152g.
- 1 ^1H NMR DMSO-d₆: δ 7.2-7.41 (m, 4H), 7.25 (s, 1H), 6.85 (d, 1H), 4.22 (m, 1H), 3.56 (m, 4H), 2.2 (s, 3H), 1.85 (m, 4H), 1.17 (d, 3H)
- 20 MS:APCI (-ve) 388

Example 159**2-[(2',4'-Dichloro-5-cyano[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid**

- 25 i) 2-(2-Bromo-4-cyanophenoxy)-(2S)-propanoic acid

Diethyl azodicarboxylate (2.12g) was added to a stirred solution of 2-bromo-4-cyanophenol (2.0g), methyl-R-lactate (1.47g) and triphenylphosphine (2.65g) in THF (80ml). After 20h, the mixture was filtered through silica using isohexane/EtOAc as solvent and the filtrate evaporated to dryness. The residue was dissolved in DCM (50ml),
 5 treated with TFA (10ml) and stirred for 2h. The solution was evaporated and the residue partitioned between EtOAc and aqueous sodium bicarbonate. The aqueous was acidified with 2M hydrochloric acid, extracted with EtOAc, dried (MgSO_4) and evaporated to give the subtitle compound.

¹H NMR DMSO-d6: δ 7.87 (s, 1H), 7.56 (d, 1H), 6.83 (d, 1H), 4.91 (q, 1H), 1.7 (d, 3H)
 10 MS:APCI (-ve) 270

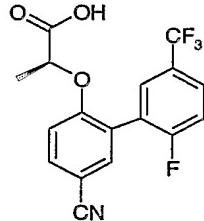
ii) 2-[(2',4'-Dichloro-5-cyano[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid

The title compound was prepared by the method of example 16 step (iii) using the product from step (i) and 2,6-dichlorophenylboronic acid.

¹H NMR DMSO-d6: δ 7.58-7.78 (m, 4H), 7.46 (d, 1H), 7.02 (d, 1H), 4.51 (q, 1H), 1.26 (d, 3H)
 15 MS:APCI (-ve) 334

Example 160

2-[[5-Cyano-2'-fluoro-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

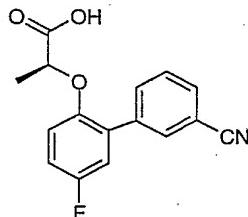


The title compound was prepared by the method of example 16 step (iii) using the product from example 159 step (i) and 3-cyanophenylboronic acid.

¹H NMR DMSO-d6: δ 7.81-8.04 (m, 4H), 7.56 (t, 1H), 7.18 (d, 1H), 5.1 (q, 1H), 1.4 (d, 3H)
 25 MS:APCI (-ve) 352

Example 161

2-[(3'-Cyano-5-fluoro[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid, sodium salt



i) 2-(2-Bromo-4-fluorophenoxy)-(2S)-propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 159 step (i) using 2-bromo-4-fluorophenol (2.5g). Yield 3.0g.

⁵ ^1H NMR DMSO-d₆: δ 7.28-7.32 (m, 1H), 6.89-6.98 (m, 1H), 6.78-6.83 (m, 1H), 4.56 (q, 1H), 1.62 (d, 3H), 1.4 (s, 9H)

ii) 2-(2-Bromo-4-fluorophenoxy)-(2S)-propanoic acid

The subtitle compound was prepared by the method of example 146 step (iv) using the product from step (i). Yield 1.2g. Carried forward to step (iii) without characterisation.

iii) 2-[3'-Cyano-5-fluoro[1,1'-biphenyl]-2-yl]oxy)-(2S)-propanoic acid, sodium salt

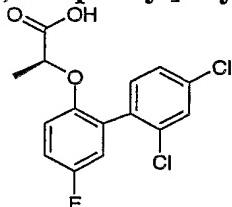
The title compound was prepared by the method of example 155 using the product from step (ii) and 3-cyanophenylboronic acid. The product was dissolved in acetonitrile, treated with 1M sodium hydroxide and evaporated to give the title compound.

¹⁵ ^1H NMR DMSO-d₆: δ 8.4 (s, 1H), 8.13 (d, 1H), 7.75 (d, 1H), 7.6 (t, 1H), 6.9-7.2 (m, 3H), 4.4 (q, 1H), 1.28 (d, 3H)

MS:APCI (-ve) 284

20 Example 162

2-[(2',4'-Dichloro-5-fluoro[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid, sodium salt



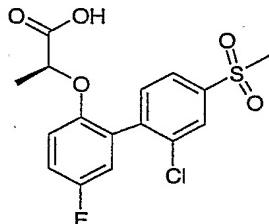
The title compound was prepared by the method of example 155 using the product from example 161 step (ii) and 2,4-dichlorophenylboronic acid. The product was dissolved in acetonitrile, treated with 1M sodium hydroxide and evaporated to give the title compound.

²⁵ ^1H NMR DMSO-d₆: δ 7.66-7.72 (m, 2H), 7.43 (d, 1H), 6.86-7.11 (m, 3H), 4.18 (q, 1H), 1.2 (d, 3H)

MS:APCI (-ve) 327

30 Example 163

2-[[2'-Chloro-5-fluoro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid



i) Benzyl 2-bromo-4-fluorophenyl ether

5 The subtitle compound was prepared by the method of example 16 step (i) using 2-bromo-4-fluorophenol and acetone as solvent. Yield 27.5g.

¹H NMR DMSO-d6: δ 7.27-7.49 (m, 6H), 6.82-6.99 (m, 2H), 5.12

ii) [2-(Benzylxy)-5-fluorophenyl]boronic acid

10 The subtitle compound was prepared by the method of example 16 step (ii) using the product from step (i). Yield 18.77g.

¹H NMR DMSO-d6: δ 7.9 (s, 2H), 7.0-7.5 (m, 8H), 5.14 (s, 2H)

iii) 2-[5-Fluoro-2-(phenylmethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

15 The subtitle compound was prepared by the method of example 146 step (i) using the product from step (ii). Yield 4.1g.

¹H NMR DMSO-d6: δ 7.58 (d, 1H), 7.29-7.4 (m, 3H), 7.26 (s, 1H), 7.04 (dt, 1H), 6.84 (d, 2H), 5.07 (s, 2H), 1.36 (s, 12H)

iv) 4-Fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

The subtitle compound was prepared by the method of example 146 step (ii) using the product from step (iii) and ethanol as solvent.

¹H NMR DMSO-d6: δ 7.63 (s, 1H), 7.2-7.27 (m, 1H), 7.01-7.08 (m, 1H), 6.8-6.83 (m, 1H), 1.37 (s, 12H)

25

v) 4-Fluoro-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]-(2S)-propanoic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 32 step (v) using the product from step (iv) and tert-butyl R-lactate. Yield 2.6g. The crude material was carried forward to step (vi).

vi) 2-[2-Borono-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid

The subtitle compound was prepared by the method of example 146 step (iv) using the product from step (v). Yield 1.65g.

MS:APCI (-ve) 227

vii) 2-[[2'-Chloro-5-fluoro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid

- 5 The title compound was prepared by the method of example 155 using the product from step (vi) and the product from example 145 step (ii).

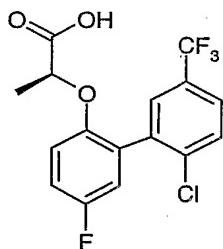
¹H NMR DMSO-d6: δ 8.06 (s, 1H), 7.86-7.93 (m, 2H), 7.03-7.23 (m, 2H), 6.9-6.97 (m, 1H), 4.43 (q, 1H), 1.24 (d, 3H)

MS:APCI (-ve) 371

10

Example 164

2-[[2'-Chloro-5-fluoro-5'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid, sodium salt



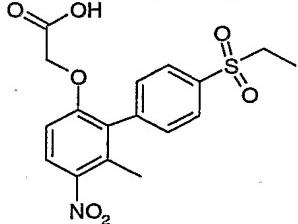
- 15 The title compound was prepared by the method of example 155 using the product from example 161 step (ii) and 2-bromo-1-chloro-4-(trifluoromethyl)benzene. The product was dissolved in acetonitrile, treated with 1M sodium hydroxide and evaporated to give the title compound. Yield 0.07g.

16 ¹H NMR DMSO-d6: δ 8.31 (bs, 1H), 7.68-7.77 (m, 2H), 7.09-7.15 (m, 2H), 6.9-6.93 (m, 1H), 4.25 (q, 1H), 1.21 (d, 3H)

MS:APCI (-ve) 361

Example 165

[[4'-(Ethylsulfonyl)-6-methyl-5-nitro[1,1'-biphenyl]-2-yl]oxy]acetic acid



25

- i) (2-Bromo-3-methyl-4-nitophenoxy)acetic acid, methyl ester
Bromine (5.27g) in acetic acid (3ml) was added dropwise to a solution of 3-methyl-4-nitrophenol (5.04g) in acetic acid (43ml) over 45mins, and then stirred for a further 1h. The solvent was evaporated, water added, extracted with ether, dried (Na2SO4) and

evaporated. The crude material was dissolved in DMF (10ml), potassium carbonate (3.79g) added, followed by methyl bromoacetate (3.37ml) and the mixture stirred at RT for 30mins and 60°C for 2h. The mixture was cooled and poured into a mixture of EtOAc and water. The organic phase was separated, washed with water, aqueous potassium carbonate and brine, dried (Na_2SO_4) and evaporated. The residue was recrystallised from toluene/isohexane. Yield 1.8g.

^1H NMR CDCl_3 : δ 7.86 (d, 1H), 6.69 (d, 1H), 4.81 (s, 2H), 3.83 (s, 3H), 2.19 (s, 3H).

(ii) [[4'-(Ethylsulfonyl)-6-methyl-5-nitro[1,1'-biphenyl]-2-yl]oxy]acetic acid, methyl ester

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) (1.78g) and 4-(ethylthio)phenylboronic acid (1.6g). Yield 2.59g.

^1H NMR CDCl_3 : δ 8.02 (d, 1H), 8.0 (d, 2H), 7.45 (d, 2H), 6.75 (d, 1H), 4.65 (s, 2H), 3.76 (s, 3H), 3.2 (q, 2H), 2.25 (s, 3H) 1.36 (t, 3H)

15

(iii) [[4'-(Ethylsulfonyl)-6-methyl-5-nitro[1,1'-biphenyl]-2-yl]oxy]acetic acid

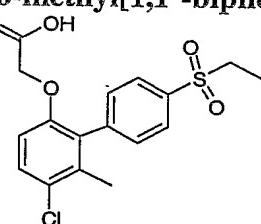
The title compound was prepared by the method of example 26 step (vi) using the product from step (ii). Yield 0.22g.

^1H NMR DMSO-d6: δ 13.16 (bs, 1H), 8.06 (d, 1H), 7.97 (d, 2H), 7.57 (d, 2H), 7.12 (d, 1H), 4.8 (s, 2H), 3.38 (q, 2H), 2.14 (s, 3H) 1.16 (t, 3H)

MS: APCI (+ve): 412 (M+MeOH+H⁺)

Example 166

[[5-Chloro-4'-(ethylsulfonyl)-6-methyl[1,1'-biphenyl]-2-yl]oxy]acetic acid



25

i) [[5-Amino-4'-(ethylsulfonyl)-6-methyl[1,1'-biphenyl]-2-yl]oxy]acetic acid, methyl ester

10% Pd/C (0.15g) was added to a solution of the product from example 165 step (ii) in EtOAc (20ml) was hydrogenated at RT and 3 bar for 2h. The mixture was filtered through celite and the filtrate evaporated to give the sub-title compound. Yield 1.4g.

^1H NMR CDCl_3 : δ 7.95 (d, 2H), 7.48 (d, 2H), 6.7 (d, 1H), 6.65 (d, 1H), 4.4 (s, 2H), 3.71 (s, 3H), 3.51 (bs, 2H), 3.18 (q, 2H), 1.88 (s, 3H) 1.34 (t, 3H)

ii) [[5-Chloro-4'-(ethylsulfonyl)-6-methyl[1,1'-biphenyl]-2-yl]oxy]acetic acid, methyl ester

Cuprous chloride (0.18g) was dissolved in acetonitrile (6ml), isopentylamine (0.24ml) added, followed by the dropwise addition of a solution of the product from step (i) in acetonitrile (6ml). The mixture was stirred for 12h, evaporated and purified by chromatography on silica eluting with 30-50% ether/isohexane. Yield 2.59g.

¹H NMR CDCl₃: δ 7.97 (d, 2H), 7.46 (d, 2H), 7.34 (d, 1H), 6.65 (d, 1H), 4.32 (s, 2H), 3.73 (s, 3H), 3.19 (q, 2H), 2.09 (s, 3H) 1.35 (t, 3H)

iii) [[5-Chloro-4'-(ethylsulfonyl)-6-methyl[1,1'-biphenyl]-2-yl]oxy]acetic acid

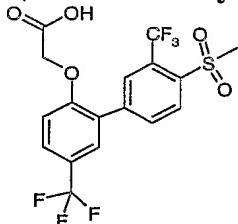
The title compound was prepared by the method of example 26 step (vi) using the product from step (ii). Purified by RPHPLC (MeCN/aqNH₄Cl). Yield 0.07g.

¹H NMR DMSO-d6: δ 7.94 (d, 2H), 7.53 (d, 2H), 7.44 (d, 1H), 6.91 (d, 1H), 4.64 (s, 2H), 3.36 (q, 2H), 2.03 (s, 3H) 1.15 (t, 3H)

MS:APCI (+ve) 367 (M+MeOH+H⁺)

Example 167

[[4'-(Methylsulfonyl)-2',5-bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid



i) 4-Bromo-1-(methylthio)-2-(trifluoromethyl)benzene

Isopentyl nitrite (0.67ml) was added dropwise to a solution of 4-bromo-2-(trifluoromethyl)aniline (1.2g) and dimethyl sulfide (0.45ml) in acetonitrile (12ml). The reaction was slowly heated to reflux and then refluxed until gas evolution ceased. The volatiles were evaporated, the residue absorbed onto silica and the product eluted off with isohexane. Yield 0.8g.

¹H NMR DMSO-d6: δ 7.59 (dd, 2H), 7.23 (d, 1H), 2.51 (s, 3H)

ii) 4,4,5,5-Tetramethyl-2-[4-(methylthio)-3-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane

Pd₂dba₃ (0.135g) and tricyclohexylphosphine (0.199g) were dissolved in dioxane (20ml) and stirred for 30min. Potassium acetate (0.867g), bis(pinacolato)diboron (1.65g) and the product from step (i) were sequentially added and the mixture heated at 90°C for 3h. The reaction was cooled, evaporated, partitioned between ether and brine, separated, dried

(Na_2SO_4) and evaporated. The residue was purified by chromatography on silica eluting with 10% ether/isohexane. Yield 0.695g.

^1H NMR DMSO-d6: δ 7.31 (d, 2H), 2.53 (s, 3H), 1.3 (s, 12H)

5 iii) 2-Bromo-4-(trifluoromethyl)phenoxyacetic acid, 1,1-dimethylethyl ester

The title compound was prepared by the method of example 1 step (i) using 2-bromo-4-(trifluoromethyl)phenol.

^1H NMR DMSO-d6: δ 6.8-7.83 (m, 3H), 4.65 (s, 2H), 1.48 (s, 9H)

10 iv) [[4'-(Methylthio)-2',5-bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid, 1,1-dimethylethyl ester

The title compound was prepared by the method of example 1 step (ii) using the products from steps (ii) and (iii). Yield 0.564g. Carried forward to step (v) without characterisation.

15 v) [[4'-(Methylsulfonyl)-2',5-bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid, 1,1-dimethylethyl ester

The product from step (iv) (0.564g) was dissolved in 50% aqueous acetone (10ml), sodium bicarbonate (0.94g) added, followed by a solution of oxone (1.5g) in water (ml) and stirred for 3h. The reaction was quenched with aqueous sodium metabisulfite, extracted with EtOAc, washed with aqueous potassium carbonate, dried (Na_2SO_4) and evaporated to give the subtitle compound. Yield 0.32g.

^1H NMR DMSO-d6: δ 8.31 (d, 1H), 8.29 (s, 1H), 8.18 (dd, 1H), 7.83 (s, 1H), 7.81 (d, 1H), 7.32 (d, 1H), 4.9 (s, 2H), 3.36 (s, 2H), 1.41 (s, 9H)

25 vi) [[4'-(Methylsulfonyl)-2',5-bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid

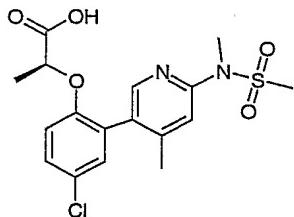
The title compound was prepared by the method of example 26 step (vi) using the product from step (v). Yield 0.2g.

30 ^1H NMR DMSO-d6: δ 8.33 (s, 1H), 8.3 (d, 1H), 8.19 (d, 1H), 7.83 (s, 1H), 7.81 (d, 1H), 7.34 (d, 1H), 4.92 (s, 2H), 3.36 (s, 2H)

MS:APCI (-ve) 441

Example 168

35 2-[4-Chloro-2-[4-methyl-6-[methyl(methylsulfonyl)amino]-3-pyridinyl]phenoxy]-(2S)-propanoic acid



i) *N*-(5-Bromo-4-methyl-2-pyridinyl)methanesulfonamide

5-Bromo-4-methylpyridin-2-amine (1.56g) was dissolved in DCM (40ml), trimethylamine (1.4ml) added, followed by methanesulfonyl chloride (1.9g) and the mixture stirred for 5 20min. The solution was washed with water, dried (MgSO_4) and evaporated. The residue was dissolved in THF, treated with TBAF, stirred for 16h and evaporated. The residue was purified by chromatography on silica eluting with 27% EtOAc/iso hexane. Yield 1.3g. Carried forward to step (ii) without characterisation.

10 ii) *N*-(5-Bromo-4-methyl-2-pyridinyl)-*N*-methylmethanesulfonamide

The product from step (i) (2.23g), potassium carbonate (2.33g) and methyl iodide (0.7ml) were stirred in DMF (20ml) for 20h. The reaction was quenched with water, extracted with EtOAc, dried (MgSO_4) and evaporated. The residue was purified by chromatography on silica eluting with 30% EtOAc/iso hexane. Yield 1.5g. Carried forward to step (ii) 15 without characterisation.

iii) 2-[4-Chloro-2-[4-methyl-6-[methyl(methylsulfonyl)amino]-3-pyridinyl]phenoxy]-(2S)- propanoic acid

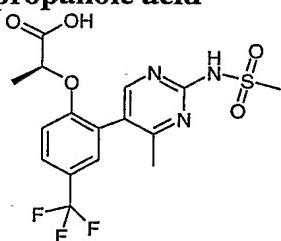
The title compound was prepared by the method of example 155 using the product from 20 step (ii) and the product from example 151 step (iv). Yield 0.125g.

^1H NMR DMSO-d6: δ 8.18 (s, 1H), 7.26-7.44 (m, 3H), 6.94 (d, 1H), 4.8 (m, 1H), 3.32 (s, 3H), 3.2 (s, 3H), 2.2 (s, 3H), 1.32 (d, 3H)

MS:APCI (-ve) 397

25 Example 169

2-[2-[4-Methyl-2-[(methylsulfonyl)amino]-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid



i) Potassium *N*-(5-bromo-4-methyl-2-pyrimidinyl)methanesulfonamide

Methanesulfonyl chloride (0.75ml) was added to a solution of 5-bromo-4-methyl-2-pyrimidinamine (1.8g) in THF (60ml), followed by the rapid dropwise addition of 1M potassium tert-butoxide/THF (20ml). After 30min the resulting precipitate was filtered off and dried. Yield 3.2g.

5 ^1H NMR DMSO-d₆: δ 8.13 (s, 1H), 2.81 (s, 3H), 2.26 (s, 3H)

ii) *N*-(5-Bromo-4-methyl-2-pyrimidinyl)-*N*-[[2-(trimethylsilyl)ethoxy]methyl] methanesulfonamide

[2-(Chloromethoxy)ethyl]trimethylsilane (0.4ml) was added to a solution of the product from step (i) in DMF (10ml) and stirred for 20min. The mixture was poured into water, extracted with ether, washed with brine, dried (MgSO_4) and evaporated. The residue was purified by chromatography on silica eluting with 20% EtOAc/isohexane. Yield 0.53g.

10 ^1H NMR DMSO-d₆: δ 8.88 (s, 1H), 5.49 (s, 2H), 3.59-3.64 (m, 5H), 2.63 (s, 3H), 0.9 (t, 2H), 0.0 (t, 9H)

15

iii) 2-[2-[4-Methyl-2-[(methylsulfonyl)[[2-(trimethylsilyl)ethoxy]methyl]amino]-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid

The title compound was prepared by the method of example 144 step (i) using the product from step (ii) and the product from example 146 step (iv). Carried forward to step (iv) without characterisation.

20 iv) 2-[2-[4-Methyl-2-[(methylsulfonyl)amino]-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid

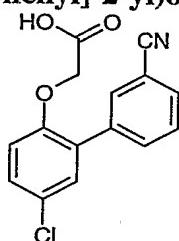
The product from step (iii) was treated with TFA (20ml) and stirred for 20min. The TFA was evaporated and the residue purified by RVHPLC ($\text{CH}_3\text{CN}/\text{aqTFA}$).

25 ^1H NMR DMSO-d₆: δ 8.84 (s, 1H), 7.77 (dd, 2H), 7.65 (d, 1H), 7.14 (d, 5H), 5.04 (q, 1H), 3.4 (s, 3H), 2.3 (s, 3H), 1.41 (d, 3H)

MS:APCI (-ve) 418

30 Example 170

[5-Chloro-3'-cyano[1,1'-biphenyl]-2-yl]oxy]- acetic acid



(i) 5'-Chloro-2'-methoxy-[1,1'-biphenyl]-3-carbonitrile

The subtitle compound was prepared by the method of example 1 step (ii) using 3-iodobenzonitrile and 5-chloro-2-methoxyphenyl boronic acid. Yield 0.465g
¹H NMR CDCl₃: δ 7.82 (1H, t), 7.71 (1H, dt), 7.62 (1H, dt), 7.51 (1H, t), 7.32 (2H, dd), 7.26 (1H, m), 6.93 (1H, d), 3.81 (3H, s)

5

(ii) 5'-Chloro-2'-hydroxy-[1,1'-biphenyl]-3-carbonitrile

A solution of boron tribromide (1M in dichloromethane, 6ml) was added to a stirred solution of the product from step (i) in dichloromethane (10ml) at 0°C. After 15min the mixture was warmed to room temperature, stirred for 16h then poured onto ice. The mixture was extracted with dichloromethane then ethylacetate, the organics combined, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 30-70% diethylether/isohexane. Yield 0.415g
¹H NMR CDCl₃: δ 7.83 (1H, s), 7.75 (1H, d), 7.68 (1H, d), 7.58 (1H, t), 7.25 (2H, m), 6.89 (1H, d), 5.00 (1H, s)

10

(iii) [(5-chloro-3'-cyano[1,1'-biphenyl]-2-yl)oxy]- acetic acid, 1,1-dimethylethyl ester

The subtitle compound was prepared by the method of example 1 step (i) using the product from step (ii). Yield 0.60g

15

¹H NMR CDCl₃: δ 7.90 (1H, s), 7.82 (1H, d), 7.63 (1H, d), 7.53 (1H, td), 7.28 (2H, m), 6.78 (1H, d), 4.52 (2H, s), 1.47 (10H, s)

(iv) [(5-Chloro-3'-cyano[1,1'-biphenyl]-2-yl)oxy]- acetic acid

The title compound was prepared by the method of example 1 step (iii) using the product from step (iii). Yield 0.265g

¹H NMR DMSO-d₆: δ 13.12 (1H, s), 8.08 (1H, s), 7.94 (1H, d), 7.82 (1H, d), 7.64 (1H, t), 7.43 (2H, m), 7.10 (1H, d), 4.78 (2H, s).

MS: APCI (-ve): 286

20

Pharmacological DataLigand Binding Assay

[³H]PGD₂ was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

25

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEKcells were grown to confluence in two layer tissue culture factories (Fisher, catalogue

number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100 μ g/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4 ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

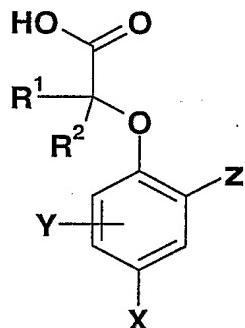
All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25 μ g membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

Each assay contained 20 μ l of 6.25nM [3 H]PGD₂, 20 μ l membrane saturated SPA beads both in assay buffer and 10 μ l of compound solution or 13,14-dihydro-15-keto prostaglandin D₂ (DK-PGD₂, for determination of non-specific binding, Cayman chemical company). Compounds and DK-PGD₂ were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at room temperature for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC₅₀ value of less than (<) 10 μ M. Specifically, example 9 has a pIC₅₀ = 7.4, example 25 has a pIC₅₀ = 8.0, and example 133 has a pIC₅₀ = 8.2.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



5

in which:

- 10 X is halogen, cyano, nitro, $S(O)_nR^6$ or C_{1-4} alkyl which is substituted by one or more halogen atoms;
- 15 Y is selected from hydrogen, halogen, CN, nitro, SO_2R^3 , OR^4 , SR^4 , SOR^3 , $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5 , $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3 , C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6} alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7 , $S(O)_nR^6$ where n is 0, 1 or 2;
- 20 Z is aryl or a ring A, where A is a six membered heterocyclic aromatic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicyclic containing one or more O, N, S atoms, the aryl or A rings all being optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, COR^9 , CO_2R^6 , SO_2R^9 , OR^9 , SR^9 , SOR^9 , $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9 , $NR^6CONR^4R^5$, $NR^6SO_2NR^4R^5$, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6} alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 , NR^6R^7 , $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7 , $SO_2NR^6R^7$ and $NR^6SO_2R^7$.
- 30 R^1 and R^2 independently represent a hydrogen atom, halogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or a C_{1-6} alkyl group, the latter four groups being optionally substituted by one or more substituents independently selected from halogen,

C₃-C₇ cycloalkyl, NR⁶R⁷, OR⁶, S(O)_nR⁶ (where n is 0, 1 or 2);

or

- 5 R¹ and R² together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR⁶ and itself optionally substituted by one or more C₁-C₃ alkyl or halogen;

10 R³ represents C₃-C₇ cycloalkyl or C₁-alkyl which may be optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0,1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

15 R⁴ and R⁵ independently represent hydrogen, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0,1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

or

20 R⁴ and R⁵ together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n (where n = 0,1 or 2), NR⁸, and itself optionally substituted by halogen or C₁-₃ alkyl;

25 R⁶ and R⁷ independently represents a hydrogen atom or C₁-C₆ alkyl;

R⁸ is hydrogen, C₁-4 alkyl, -COC₁-C₄ alkyl, CO₂C₁-C₄alkyl or CONR⁶C₁-C₄alkyl;

30 R⁹ represents aryl, heteroaryl, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, aryl, heteroaryl OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

35 R¹⁰ and R¹¹ independently represent aryl or heteroaryl, hydrogen, C₃-C₇ cycloalkyl or C₁-alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C₃-C₇ cycloalkyl, aryl, heteroaryl, OR⁶ and NR⁶R⁷, S(O)_nR⁶ (where n = 0, 1 or 2), CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷ and NR⁶SO₂R⁷;

or

R¹⁰ and R¹¹ together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocyclic ring optionally containing one or more atoms selected from O, S(O)_n (where n = 0, 1 or 2), NR⁸, and itself optionally substituted by halogen or 5 C₁-C₃ alkyl.

2. A compound according to claim 1 in which X is halogen, cyano, nitro, S(O)_nR⁶ or C₁₋₄alkyl which is substituted by one or more halogen atoms;
- 10 3. A compound according to claim 1 in which X is trifluoromethyl, nitro, cyano or halogen.
4. A compound according to any one of claims 1 to 3 in which Y is hydrogen, halogen or C₁₋₃alkyl.
- 15 5. A compound according to any one of claims 1 to 4 in which Z is phenyl, pyridinyl, pyrimidyl, naphthyl, quinolyl, benzo[b]thienyl or benzofuranyl each optionally substituted with substituents as defined in claim 1.
- 20 6. A compound according to any one of claims 1 to 4 in which Z is phenyl optionally substituted with substituents as defined in claim 1.
7. A compound according to any one of claims 1 to 6 in which both R¹ and R² are hydrogen or one is hydrogen and the other is methyl or ethyl or both are methyl.
- 25 8. A compound according to any one of claims 1 to 7 selected from:
 {[5-Chloro-4'-(ethylthio)biphenyl-2-yl]oxy}acetic acid
 {[5-Chloro-4'-(ethylsulfonyl)biphenyl-2-yl]oxy}acetic acid
 [(4',5-Dichlorobiphenyl-2-yl)oxy]acetic acid
 [(5-Chloro-4'-cyanobiphenyl-2-yl)oxy]acetic acid
 [(5-Chloro-4'-methoxybiphenyl-2-yl)oxy]acetic acid
 (4-Chloro-2-quinolin-8-ylphenoxy)acetic acid,
 [(5-Chloro-3',4'-dimethoxybiphenyl-2-yl)oxy]acetic acid
 2'-(Carboxymethoxy)-5'-chlorobiphenyl-4-carboxylic acid
 30 {[5-Chloro-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid
 {[5-Chloro-4'-(ethylsulfonyl)-2'-methylbiphenyl-2-yl]oxy}acetic acid
 [(5-Cyanobiphenyl-2-yl)oxy]acetic acid
 [(5-Nitrobiphenyl-2-yl)oxy]acetic acid
 {[4'-(Methylthio)-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid

- {[4'-(Methylsulfonyl)-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid,
{[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)biphenyl-2-yl]oxy}acetic acid
(4-Chloro-2-pyrimidin-5-ylphenoxy)acetic acid,
{2-[5-(Aminosulfonyl)pyridin-2-yl]-4-chlorophenoxy}acetic acid
5 [2-(2-Aminopyrimidin-5-yl)-4-chlorophenoxy]acetic acid, trifluoroacetate salt
[4-Chloro-2-(4-methyl-2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetic acid
{4-Chloro-2-[2-(dimethylamino)pyrimidin-5-yl]phenoxy}acetic acid
[4-Chloro-2-(2-morpholin-4-ylpyrimidin-5-yl)phenoxy]acetic acid
{4-Chloro-2-[2-(methylamino)pyrimidin-5-yl]phenoxy}acetic acid
10 {2-[2-(Benzylamino)pyrimidin-5-yl]-4-chlorophenoxy}acetic acid
[4-Chloro-2-(2-piperidin-1-ylpyrimidin-5-yl)phenoxy]acetic acid
(4-Chloro-2-{2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}phenoxy)acetic acid
[[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
15 [[5-Chloro-4'-(ethylsulfonyl)-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-(Ethylsulfonyl)-2'-fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-acetic acid,
[[5-Chloro-4'-(ethylsulfonyl)-2'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
2-[[5-Chloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-propanoic acid
2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-
20 propanoic acid
2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2R)-
propanoic acid,
2-[[2',5-Dichloro-4'-(ethylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)- propanoic acid,
2-[[2'-Chloro-4'-(ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-
25 propanoic acid
2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-2-methyl-
propanoic acid,
2-[[4'-(Ethylsulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-butanoic
acid,
30 [4-Chloro-2-[2-[(methylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic
acid
[4-Chloro-2-[2-[(ethylsulfonyl)(phenylmethyl)amino]-5-pyrimidinyl]phenoxy]-acetic acid
[2-[2-[Acetyl(phenylmethyl)amino]-5-pyrimidinyl]-4-chlorophenoxy]-acetic acid
[[4'-(Ethylsulfonyl)-5-fluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid
35 [[4'-(Ethylsulfonyl)-4,5-difluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid
[[4'-(Ethylsulfonyl)-3,5-difluoro-2'-methyl[1,1'-biphenyl]-2-yl]oxy]-acetic acid
[2-(2-Amino-5-methyl-3-pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[4'-Amino-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Amino-2'-chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

- [[2'-Chloro-4'-hydroxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(2,4-Dimethoxy-5-pyrimidinyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[2'-Chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2',5-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
5 [[5'-Fluoro-2'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[5'-Cyano-2'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2',5'-Dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
10 [[5'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2'-Fluoro-6'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-[(Ethylamino)carbonyl]amino]-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-
15 yl]oxy]- acetic acid
[[2'-Methyl-4'-[(methylamino)carbonyl]amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-
yl]oxy]- acetic acid
[[4'-[(Cyclopropylamino)carbonyl]amino]-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-
yl]oxy]- acetic acid
[[2'-Methyl-4'-[(propylamino)carbonyl]amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-
yl]oxy]- acetic acid,
20 [[2',4'-Dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[5'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-(Aminocarbonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Fluoro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2',5'-Difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
25 [[5'-(Aminosulfonyl)-2'-chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Cyano-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Chloro-2'-fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2',5'-Difluoro-4'-methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2'-fluoro-5'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
30 [[2'-Fluoro-4'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Methoxy-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-(Aminosulfonyl)-2',5'-difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic
acid
[2-Benzo[b]thien-3-yl-4-(trifluoromethyl)phenoxy]- acetic acid
35 [[2-(2-Benzofuranyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[4'-Chloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-(1-Methylethyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3',4'-Difluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(1,3-Benzodioxol-5-yl)-4-(trifluoromethyl)phenoxy]- acetic acid

- [[4'-Ethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Fluoro-5-(trifluoromethyl)[1,1':4',1"-terphenyl]-2-yl]oxy]- acetic acid
[[4'-(Trifluoromethoxy)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2',3'-Dichloro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
5 [[4'-(1,1-Dimethylethyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(6-Methoxy-2-naphthalenyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[4'-(Eethylthio)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Acetyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(2-Chloro-5-methyl-4-pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid,
10 [[5'-(Aminosulfonyl)-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid,
[2-(8-Quinolinyl)-4-(trifluoromethyl)phenoxy]- acetic acid,
[[3'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid,
[2-[4-Methyl-6-[methyl(methylsulfonyl)amino]-3-pyridinyl]-4-(trifluoromethyl) phenoxy]-
acetic acid,
15 [[2'-Methyl-5'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid,
2'-(Carboxymethoxy)-5'-(trifluoromethyl)- [1,1'-biphenyl]-3-carboxylic acid, 3-methyl
ester
2'-(Carboxymethoxy)-5'-(trifluoromethyl)- [1,1'-biphenyl]-2-carboxylic acid, 2-methyl
ester
20 [[5-(Trifluoromethyl)[1,1':4',1"-terphenyl]-2-yl]oxy]- acetic acid
[[3'-Fluoro-2',4'-dimethyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2'-Nitro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid,
[[2'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Chloro-2'-methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
25 [[5-(Trifluoromethyl)[1,1':3',1"-terphenyl]-2-yl]oxy]- acetic acid
2'-(Carboxymethoxy)-5'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxylic acid, 4-methyl
ester
[[4'-Nitro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[5-(Trifluoromethyl)-3'-[(trifluoromethyl)thio][1,1'-biphenyl]-2-yl]oxy]- acetic acid
30 [[5-(Trifluoromethyl)-4'-[(trifluoromethyl)thio][1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Methyl-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
35 [[2-(3-Pyridinyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[2'-Fluoro-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[2'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Methoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid

- [[3'-(Ethylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[3'-Propoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-Propoxy-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(2-Amino-4-methyl-5-pyrimidinyl)-4-(trifluoromethyl)phenoxy]- acetic acid
5 [[4'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4',5-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-(2-Naphthalenyl)-4-(trifluoromethyl)phenoxy]- acetic acid
[[4'-(1-Pyrrolidinylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-(Dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
10 [[4'-[[(Phenylmethyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-[[(2,2,2-Trifluoroethyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-
acetic acid
[[4'-[[(5-Methyl-2-thiazolyl)amino]sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-
15 acetic acid
[[4'-[[(Phenylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-[[(Diethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-[[(Cyclopropylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-(Aminosulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
20 [[4'-[[(Methylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[[4'-[[(4-Methyl-1-piperazinyl)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]- acetic acid
[2-[4-Methyl-2-(5-methyl-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid
25 [2-[4-Methyl-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid
[2-[2-(1,1-Dioxido-2-isothiazolidinyl)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid, ammonium salt
[2-[2-(3-Hydroxy-1-azetidinyl)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-
30 acetic acid
[2-[4-Methyl-2-(4-methyl-1-piperazinyl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-
acetic acid
[2-[4-Methyl-2-(1-pyrrolidinyl)-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid
[2-[2-(Dimethylamino)-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid
35 [2-[5-Methyl-2-[methyl(methylsulfonyl)amino]-4-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-
acetic acid
[2-[2-[(Dimethylamino)sulfonyl]amino]-4-methyl-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]- acetic acid

- [[2'-Chloro-4'-(methoxycarbonyl)amino]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid
- 2-[[2'-Chloro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 5 2-[[3'-Cyano-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 2-[[4'-(Dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 2-[[2'-Chloro-4'-(dimethylamino)sulfonyl]-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 10 2-[[2'-Fluoro-4'-(methylsulfonyl)-5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- [[2',5-Dichloro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- [[5-Chloro-4'-(dimethylamino)sulfonyl][1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- [[2',5-Dichloro-4'-(dimethylamino)sulfonyl][1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 15 [(5-Chloro-3'-cyano[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid
- [[5-Chloro-4'-(dimethylamino)sulfonyl]-2'-fluoro[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- [[5-Chloro-4'-(4-morpholinylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- [[5-Chloro-2'-fluoro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 20 2-[[4'-(1-Azetidinylsulfonyl)-5-chloro[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 2-[[5-Chloro-2'-methyl-4'-(1-pyrrolidinylcarbonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid,
- 2-[(2',4'-Dichloro-5-cyano[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid
- 2-[[5-Cyano-2'-fluoro-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 25 2-[(3'-Cyano-5-fluoro[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid, sodium salt
- 2-[(2',4'-Dichloro-5-fluoro[1,1'-biphenyl]-2-yl)oxy]-(2S)-propanoic acid, sodium salt
- 2-[[2'-Chloro-5-fluoro-4'-(methylsulfonyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid
- 2-[[2'-Chloro-5-fluoro-5'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]-(2S)-propanoic acid,
- [[4'-(Ethylsulfonyl)-6-methyl-5-nitro[1,1'-biphenyl]-2-yl]oxy]acetic acid
- 30 [[5-Chloro-4'-(ethylsulfonyl)-6-methyl[1,1'-biphenyl]-2-yl]oxy]acetic acid
- [[4'-(Methylsulfonyl)-2',5-bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]oxy]acetic acid
- 2-[4-Chloro-2-[4-methyl-6-[methyl(methylsulfonyl)amino]-3-pyridinyl]phenoxy]-(2S)-propanoic acid
- 2-[2-[4-Methyl-2-[(methylsulfonyl)amino]-5-pyrimidinyl]-4-(trifluoromethyl)phenoxy]-(2S)-propanoic acid
- 35 [(5-Chloro-3'-cyano[1,1'-biphenyl]-2-yl)oxy]- acetic acid
and pharmaceutically acceptable salts thereof.

9. A compound of formula (I) according to any one of claims 1 to 8 for use in therapy.

10. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I),
5 or a pharmaceutically acceptable salt as defined in claims 1 to 8.

11. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 8.
10

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE2004/000535**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **10-11**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/000535

Claims 10-11 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000535

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 317/22, C07C 317/28, C07C 59/48, C07D 215/18, C07D 239/24,
C07D 213/71, A61K 31/10, A61K 31/192

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0160807 A1 (MERCK & CO. INC.), 23 August 2001 (23.08.2001) --	1-11
A	GB 1356834 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED), 19 June 1974 (19.06.1974) --	1-11
A	EP 1170594 A2 (PFIZER PRODUCTS INC.), 9 January 2002 (09.01.2002) -----	1-11

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 July 2004

Date of mailing of the international search report

14 -07- 2004

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

Göran Karlsson/EÖ
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

30/04/2004

PCT/SE 2004/000535

WO	0160807	A1	23/08/2001	AU	3821401 A	27/08/2001
				CA	2400021 A	23/08/2001
				EP	1259494 A	27/11/2002
				JP	2003523336 T	05/08/2003
				US	6569879 B	27/05/2003
				US	2002173663 A	21/11/2002

GB	1356834	A	19/06/1974	AR	198064 A	31/05/1974
				AR	203626 A	30/09/1975
				AR	203627 A	30/09/1975
				AT	100174 A	15/06/1975
				AT	100274 A	15/06/1975
				AT	320633 B	25/02/1975
				AT	328431 B	25/03/1976
				AT	328432 B	25/03/1976
				AU	464145 B	14/08/1975
				AU	4738172 A	11/04/1974
				BE	790679 A	27/04/1973
				CA	983932 A	17/02/1976
				CH	577499 A	15/07/1976
				CS	178120 B	31/08/1977
				CS	178144 B	31/08/1977
				DD	105611 A	05/05/1974
				DE	2253927 A	10/05/1973
				EG	11358 A	28/02/1977
				ES	408226 A	01/02/1976
				ES	437311 A	01/04/1977
				FR	2158464 A,B	15/06/1973
				HU	169711 B	28/02/1977
				IE	37998 B,L	07/12/1977
				IL	40521 A	25/06/1975
				JP	48056667 A	09/08/1973
				NL	7214807 A	07/05/1973
				PH	10303 A	10/11/1976
				SE	384856 B,C	24/05/1976
				SU	527135 A	30/08/1976
				SU	577980 A	25/10/1977
				US	3884919 A	20/05/1975
				US	4012513 A	15/03/1977
				ZA	7207007 A	27/06/1973
				AT	100374 A	15/06/1975
				AT	328433 B	25/03/1976

EP	1170594	A2	09/01/2002	IL	144101 D	00/00/0000
				JP	2002098702 A	05/04/2002
				JP	2004004109 A	08/01/2004
				US	2002022218 A	21/02/2002